CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-055

MEDICAL REVIEW

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

Date: April 12, 2007

From: Lisa L. Mathis, M.D., Associate Director
Pediatric and Maternal Health Staff
Office of New Drugs

To: Edward Cox, M.D., M.P.H., Director (acting)
Office of Antimicrobial Products

With majority contribution from: Robert "Skip" Nelson, MD PhD
Pediatric Ethicist,
Office of Pediatric Therapeutics
Office of the Commissioner,
Food and Drug Administration

Re: Altabax (AKA SB-275833, retapamulin) topical ointment for the treatment of impetigo
Sponsor: GlaxoSmithKline
Current Indication: Not approved. Action date 4/12/07
Proposed Indication: Impetigo caused by Staphylococcus aureus and Streptococcus pyogenes
Study Phase: PHASE 3

Background: We were requested to review the protocol for this study, the results of which were submitted for the approval of Altabax for the treatment of impetigo in adult and pediatric. The main question to address was the ethics of conducting a placebo controlled trial in patients with this condition.

Robert "Skip" Nelson, M.D. Ph.D., Pediatric Ethicist, Office of Pediatric Therapeutics Office of the Commissioner, Food and Drug Administration, reviewed the protocol and sent comments to Dr. Edward Cox, 4/11/07.

Protocol: Number TOC103469
A Randomized, Double-blind, Multicenter, Superiority, Placebo controlled, Phase 3 Study to Assess the Safety and Efficacy of Topical 1% retapamulin (Altabax) Ointment versus Placebo Ointment Applied Twice Daily for 5 days in the Treatment of Adults and Pediatric Patients with Impetigo

Objective: To compare the safety and efficacy of topical application of 1% retapamulin ointment with vehicle applied twice daily for 5 days, in the treatment of adult and pediatric subjects with impetigo.

Number of Patients: 140 active and 70 placebo

Ages of Subjects for Inclusion: All

Conclusion:
(Paraphrased from Dr. Nelson's e-mail to Dr. Edward Cox, 4/11/07)
After review of the protocol, it appears that the study was appropriately designed, and the inclusion of a placebo control group was both ethical and consistent with the FDA pediatric regulations - Subpart D, ICH E6 and E10. Here are the reasons, in brief.

There was equipoise between the investigational product and placebo, and the preclinical and adult data suggested that both arms had an appropriate balance of risk and benefit. The study is thus approvable under 21 CFR 50.52. In fact, the published rate of 59% cure for placebo cited in the protocol would argue for the methodological inclusion of a placebo control.

Even if there was not equipoise, the withholding of a proven effective treatment from the placebo control group met the criteria of (a) a minor condition (for which many physicians would observe while using non-medication measures) where (b) withholding a proven medication would only result in temporary and minor discomfort. These are the conditions for withholding a proven treatment in favor of a placebo control in both ICH E-10 Choice of Control Group and in the revised Declaration of Helsinki (since 2002).

The risk to the placebo group was no more than a minor increase over minimal risk (given the condition and study design) and thus would be acceptable under 21 CFR 50.53 even if there was no prospect of direct benefit (which, of course, was not true given the potential 59% placebo response cure rate).

The protocol included multiple measures to minimize risk to all of the study participants: lesion amenable to topical treatment, early failure or withdrawal allowed, an optional visit provided for evaluation of this possibility, daily telephone contact, and overall close follow-up.

Therefore, there are not ethical problems with this study from Dr. Nelson's perspective.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lisa Mathis
4/12/2007 12:26:23 PM
MEDICAL OFFICER

Acting Office Director Memo

NDA#s: [redacted]
22-055 for Impetigo

Applicant: GlaxoSmithKline

Drug: retapamulin ointment

Formulation: ointment, 1%

Proposed Trade Name: Altabax

Applicant's Proposed Indications

[redacted]

(NDA 22-055, June 12, 2006)
ALTABAX is indicated for the topical treatment of the following uncomplicated skin and skin structure infections (SSSI) due to *Staphylococcus aureus* (methicillin-susceptible isolates only) or *Streptococcus pyogenes* (see CLINICAL STUDIES):

[redacted]

- Impetigo; up to 100 cm^2 in total area (up to 10 lesions)

Applicant's Proposed Dosage Regimen: A thin layer of Altabax ointment should be applied to the affected area twice daily for 5 days. The treated area may be covered with a sterile bandage or gauze dressing if desired.

[redacted]

NDA 22-055
Date of Submission: June 12, 2006
PDUFA Goal Date: April 12, 2007

Regulatory Action:

[redacted]

Approval for NDA 22-055 (Impetigo)

Summary of Key Deficiencies

[redacted]

This memorandum is written to document my decision on the regulatory actions for [redacted] NDA 22-055, retapamulin 1% ointment for [redacted] impetigo. I have considered the reviews prepared for NDA 22-055 [redacted]. Please see also my previous memo for [redacted] dated December 22, 2006.

The reader is also referred to the individual reviews for the details of the discipline specific reviews including the Chemistry, Pharmacology/Toxicology, Microbiology, Clinical Pharmacology and Biopharmaceutics, Statistical and Medical Officer's reviews.

Background

Retapamulin is a semisynthetic pleuromutilin antibiotic that inhibits protein synthesis. The applicant has studied retapamulin 1% ointment for the related uncomplicated skin and skin structure infections of [redacted] impetigo (NDA 22-055). [redacted] previously received an approvable action on December 22, 2006. [redacted] This memo addresses NDA 22-055 [redacted]

Chemistry

[redacted]

Dr. Matecka also provides a review for NDA 22-055. The CMC reviewers recommend approval from the standpoint of chemistry. The facilities inspections have been completed and were acceptable.

Pharmacology / Toxicology

[redacted] As noted in Dr. Rafie-Koplin's review of NDA 22-055, no new nonclinical studies were included in NDA 22-055.

Clinical Pharmacology and Biopharmaceutics

The clinical pharmacology of retapamulin is discussed in Dr. Bonapace's Clinical Pharmacology and Biopharmaceutics (CPB) Review [redacted]. The recommendation from the CPB standpoint is that retapamulin is acceptable. The CPB review notes that the amounts of retapamulin detectable in plasma were related to the surface area of exposure and whether the skin was intact or abraded (abraded skin leading to greater exposure). The reviewer notes that "following application of retapamulin ointment, 1% twice daily for 5 days to adult patients (≥18 yrs of age) with uncomplicated bacterial skin infections (maximum lesion size of 100 cm^2 or 10 cm in length; maximum amount of drug applied per dose to a subject was 10 mg per cm^2), systemic absorption was minimal and plasma concentrations of retapamulin were generally below the lower limit of quantitation. Only 9 out of 355 samples (7 out of 35 subjects) had measurable retapamulin concentrations ranging from 0.5 to 4.3 ng/mL. There was no accumulation with repeat administration (twice daily for 5 days).

Analyses of ECGs from healthy subjects after topical administration of retapamulin on intact and abraded skin did not show significant effects on the QT/QTc interval. The I/Ki ratios were less than 0.1 for all cytochrome P450 isoenzymes; hence, no clinical relevant drug interactions are anticipated. The mean AUC_{0-24} and C_{max} of retapamulin increased 80 and 70% respectively when retapamulin was administered with ketoconazole, a strong CYP3A4 inhibitor. Because of the minimal degree of absorption for retapamulin, no dosage adjustment is recommended when retapamulin is co-administered with CYP3A4 inhibitors.

Data on a concentration-effect relationship of retapamulin (0.1, 0.5, 1, 2, and 5% along with a placebo and untreated control) in an animal model of surgical wound infection with *S. aureus* and *S. pyogenes* is also provided in the NDA. The results showed substantial reductions of bacterial counts for retapamulin treated animals compared to untreated and placebo treated animals for the 1, 2, and 5% concentrations. The effect also appeared to be less in the lower retapamulin concentrations (e.g., 0.1%) compared with the higher concentrations, supporting a concentration-effect relationship in this animal model of wound infection.

[redacted]

Microbiology

The recommendation from the microbiology reviewer is that the indication of [redacted] impetigo could be approved from the standpoint of microbiology. The microbiology review notes that studies evaluating the antimicrobial activity of retapamulin show that in vitro it inhibits the growth of gram-positive bacteria such as *S. aureus* and *S. pyogenes* (the two common pathogens in skin infections) at low

concentrations (0.3 to 0.5 mcg/mL). The reviewer also notes a decrement in clinical efficacy for methicillin-susceptible *S. aureus* that are positive for the Panton-Valentine Leukocidin (PVL) gene, but the absence of a difference in susceptibility based upon the presence or absence of the PVL gene [redacted]. Although inclusion of methicillin-resistant *S. aureus* (MRSA) was not requested, the microbiology review also notes a decrement in clinical efficacy for retapamulin for MRSA.

Clinical Efficacy

Impetigo

Data are provided from two phase 3 studies in patients with impetigo. The first of these is a placebo controlled study (Study 103469). The second study is an active controlled study comparing retapamulin to sodium fusidate ointment (Study 100224).

Study 103469 was a randomized (2:1) multi-center double-blind study comparing retapamulin to placebo in patients with impetigo of ages 9 months or greater including adults. Retapamulin ointment was administered twice daily for five days. Baseline demographic features were reasonably well-balanced across the treatment arms at baseline. In the placebo group there was a greater proportion of patients that withdrew from the study for lack of efficacy or disease progression. The results for clinical response at the end of therapy visit on day 7 and the follow-up visit on day 14 are summarized in Table 1.

Table 1. Clinical Response at End of Therapy and at Follow-up by Analysis Population

Study 103469

Analysis Population	Altabax		Placebo		Difference in Success Rates (%)	95 % CI (%)
	n/N	Success Rate (%)	n/N	Success Rate (%)		
End of Therapy						
PPC	111/124	89.5	33/62	53.2	36.3	(22.8, 49.8)
ITTC	119/139	85.6	37/71	52.1	33.5	(20.5, 46.5)
PPB	96/107	89.7	26/52	50.0	39.7	(25.0, 54.5)
ITTB	101/114	88.6	28/57	49.1	39.5	(25.2, 53.7)
Follow Up						
PPC	98/119	82.4	25/58	43.1	39.2	(24.8, 53.7)
ITTC	105/139	75.5	28/71	39.4	36.1	(22.7, 49.5)
PPB	86/102	84.3	18/48	37.5	46.8	(31.4, 62.2)
ITTB	91/114	79.8	19/57	33.3	46.5	(32.2, 60.8)

n = number with clinical success outcome, N = number in analysis population
PPC = Clinical Per Protocol Population, ITTC = Clinical Intent to Treat Population, PPB = Bacteriological Per Protocol Population, ITTB = Bacteriological Intent to Treat Population

The results show superiority of retapamulin over placebo and provide strong evidence of the efficacy in impetigo. The per pathogen response rates from study 103469 are summarized in table 2. Study 103469 did not provide data on patients with methicillin-resistant *Staphylococcus aureus*.

Table 2. Clinical Response at End of Therapy and Follow-Up for Patients with *Staphylococcus aureus* and *Streptococcus pyogenes* at Baseline in the Clinical Intent to Treat Population (ITTC) – Study 103469

Pathogen	Retapamulin		Placebo	
	n/N	Success Rate (%)	n/N	Success Rate (%)
End of Therapy				
Staphylococcus aureus (Methicillin-susceptible)	84/95	88.4	27/51	52.9
Streptococcus pyogenes	30/34	88.2	3/8	37.5
Follow Up				
Staphylococcus aureus (Methicillin-susceptible)	75/95	78.9	18/51	35.3
Streptococcus pyogenes	29/34	85.3	1/8	12.5

n = number with clinical success outcome, N = number in analysis population

Study 103469 was a placebo controlled study. In order to minimize risk the protocol inclusion and exclusion criteria selected for a patient population with impetigo appropriate for topical therapy, included an optional visit and provisions for early withdrawal in the setting of treatment failure or disease progression, and daily telephone contact. The study protocol has been evaluated by a Pediatric ethicist at the FDA and found that the study was appropriately designed and ethical.

The second study (study 100224) was randomized, single-blind, multicenter study comparing retapamulin to sodium fusidate ointment that enrolled patients ages 9 months of age or greater including adults. Sodium fusidate ointment is not an approved comparator. The division previously informed the sponsor that showing non-inferiority to a non-approved comparator could not serve as a pivotal study. The results for study 100224 are summarized in table 3.

Table 3. Clinical Response at End of Therapy and at Follow-up by Analysis Population – Study 100224

	Retapamulin		**Sodium Fusidate**		**Difference in Success Rates (%)**	**95 % CI (%)**
	n/N	**Success Rate (%)**	**n/N**	**Success Rate (%)**		
End of Therapy						
PPC	314/317	99.1	141/150	94.0	5.1	(1.1, 9.0)
ITTC	327/345	94.8	155/172	90.1	4.7	(-0.4, 9.7)
PPB	240/242	99.2	106/114	93.0	6.2	(0.5, 12.6)
ITTB	250/263	95.1	116/131	88.5	6.5	(1.4, 11.0)
Follow Up						
PPC	297/308	96.4	134/143	93.7	2.7	(-1.8, 7.2)
ITTC	310/345	89.9	150/172	87.2	2.6	(-3.3, 8.6)
PPB	227/235	96.6	99/107	92.5	4.1	(-1.4, 9.6)

ITTB	237/263	90.1	111.131	84.7	5.4	(-1.8, 12.5)

n = number with clinical success outcome, N = number in analysis population, PPC = Clinical Per Protocol Population, ITTC = Clinical Intent to Treat Population, PPB = Bacteriological Per Protocol Population, ITTB = Bacteriological Intent to Treat Population

The applicant also provided information from the medical literature supporting that sodium fusidate ointment is an active compound. Hence the findings from study 100224, given the point estimates and associated confidence intervals provide supportive evidence of the efficacy of retapamulin.

The per pathogen outcomes from study 100224 are summarized in table 4. There were a limited number of patients with MRSA in the study.

Table 4. Clinical Response at End of Therapy and Follow-Up for Patients with *Staphylococcus aureus* and *Streptococcus pyogenes* at Baseline in the Clinical Per Protocol Population (PPC) – Study 100224

Pathogen	Retapamulin		Sodium Fusidate	
	n/N	Success Rate (%)	n/N	Success Rate (%)
End of Therapy				
Staphylococcus aureus	209/211	99.1	90/97	92.8
Methicillin-susceptible	201/203	99.0	88/95	92.6
Methicillin-resistant	8/8	100	2/2	100
Streptococcus pyogenes	90/92	97.8	32/36	88.9
Follow Up				
Staphylococcus aureus	199/206	96.6	83/90	93.3
Methicillin-susceptible	191/198	96.5	81/88	92.0
Methicillin-resistant	8/8	100	2/2	100
Streptococcus pyogenes	87/91	95.6	31/36	86.1

n = number with clinical success outcome, N = number in analysis population

Studies 103469 and 100224 were conducted outside of the US. The data these studies provided on patients with impetigo is relevant to the U.S. population. DSI performed inspections of two study sites in study 103469 (see the section on DSI inspections in this memo). As noted previously the study protocol for study 103469, the placebo controlled study has been reviewed by a pediatric ethicist at FDA and found to be of appropriate design, ethical and consistent with FDA pediatric regulations – subpart D.

The results from study 103469 and the supportive findings from study 100224 provide evidence of the efficacy of retapamulin for the treatment of impetigo due to methicillin-sensitive *S. aureus* or *S. pyogenes* in patients 9 months of age or older.

[redacted]

2 Page(s) Withheld

X Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical- 1

Across the phase 3 studies there were 2,115 adult and pediatric patients who used at least one dose of retapamulin. The most common drug-related adverse events reported (≥1% of patients) were application site irritation (1.4%) in the retapamulin group, diarrhea (1.7%) in the cephalexin group, and application site pruritis (1.4%) and application site paresthesia (1.4%) in the placebo group. The most common adverse events reported in (≥1% of subjects) in the adult and pediatric patients are summarized in the tables 5 and 6.

Table 5. Adverse Events Reported by ≥1% of Adult Patients Treated With Altabax in Phase 3 Clinical Studies

Adverse Event	Altabax N = 1527 %	Cephalexin N = 698 %
Headache	2.0	2.0
Application site irritation	1.6	<1.0
Diarrhea	1.4	2.3
Nausea	1.2	1.9
Nasopharyngitis	1.2	<1.0
Creatinine phosphokinase increased	<1.0	1.0

Table 6. Adverse Events Reported by ≥1% in Pediatric Patients Aged 9 Months to 17 Years Treated With Altabax in Phase 3 Clinical Studies

Adverse Event	Altabax N = 588 %	Cephalexin N = 121 %	Placebo N = 64 %
Application site pruritus	1.9	0	0
Diarrhea	1.7	5.0	0
Nasopharyngitis	1.5	1.7	0
Pruritus	1.5	1.0	1.6
Eczema	1.0	0	0
Headache	1.2	1.7	0
Pyrexia	1.2	<1.0	1.6

DSI Inspections

[redacted] DSI inspections of two sites (both outside of the U.S.) were performed as part of the review of NDA 22-055. As noted in the DSI Clinical Inspection Summary of 3/21/07 the data from the sites may be used in support of the impetigo indication. The summary also notes that hematological evaluation was not available from 18 subjects and that minor regulatory violations with respsect to record keeping were noted.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Edward Cox
4/12/2007 07:45:17 PM
MEDICAL OFFICER

CLINICAL TEAM LEADER MEMO

Application Type	1. NDA
	[redacted]
Submission Number	1. 22-055
	[redacted]
Submission Code	1. N-000
	[redacted]
Letter Date	1. June 12, 2006
	[redacted]
Stamp Date	1. June 12, 2006
	[redacted]
PDUFA Goal Date	1. April 12, 2007
	[redacted]
Reviewer Name	Jean Mulinde, M.D.
Review Completion Date	March 25, 2007
Established Name	Retapamulin Ointment, 1%
(Proposed) Trade Name	Altabax
Therapeutic Class	Topical anti-infective
Applicant	GlaxoSmithKline
Priority Designation	S
Formulation	Ointment
Dosing Regimen	Topical
Indications	[redacted]
	Impetigo
Intended Population	Pediatric >= 9 months of age and Adult patients

Appears This Way
On Original

1. Regulatory History

[redacted]

On July 11, 2005 a Pre-NDA meeting was held with the Division and Office of Antimicrobial Products and Applicant representatives present. Issues discussed included submission of safety data from overseas impetigo studies, MRSA response data, analyses of data in which *Staphylococcus aureus* containing the PVL gene was looked as specifically, requirements for sub-analysis of patients with exudate/pus at follow-up, pediatric studies and submission of safetv data.

[redacted]

On February 28, 2006 GlaxoSmithKline (GSK) submitted a request for a Pre-NDA meeting to discuss the planned submission of a second NDA for retapamulin ointment, 1% that would contain results from two impetigo studies that had been conducted outside of the U.S. The studies included a placebo controlled study and a non-inferiority study, in which retapamulin ointment was compared to topical sodium fusidate (Note: fusidic acid is not an approved drug product, in any form, in the U.S.). This was the first communication submitted to the Agency in which the Applicant identified their intention to seek approval for retapamulin ointment, 1% for the indication of impetigo.

On May 8, 2006 the Pre-NDA meeting for the second NDA (NDA 22-055) for retapamulin ointment, 1% was held.

On June 12, 2006 NDA 22-055 was submitted, containing data from the two foreign studies mentioned above; in this NDA the Applicant requests approval for retapamulin ointment, 1% for the treatment of impetigo.

[redacted]

The background package included:

1. A summary of clinical and bacteriological outcomes in the placebo group of the GSK-sponsored study 103469 (a double-blind, randomized, placebo-controlled study of patients with impetigo)
2. [redacted]
3. A discussion of clinical and bacteriological outcomes in a study comparing fusidic acid cream versus placebo for treatment of impetigo (Koning et al. 2002)
4. A discussion of clinical and bacteriological outcomes in a study comparing mupirocin ointment versus vehicle for treatment of impetigo (Rojas et al. 1984)
5. A discussion of clinical and bacteriological outcomes in a study comparing mupirocin ointment versus placebo for treatment of patients with uncomplicated skin and skin structure infections (Gould et al. 1984)
6. A discussion of clinical and bacteriological outcomes in a single phase 3 study comparing mupirocin ointment versus Bactroban Ointment in patients with impetigo (NDA 50-788 for Mupirocin Ointment, Clay-Park Laboratories), which was approved by FDA on December 4, 2002. The Applicant sponsored one randomized, double-blind, active-controlled clinical trial to assess the non-inferiority of mupirocin ointment versus Bactroban Ointment where each product was applied three times a day for 7 days by patients with impetigo. The study was conducted between April 2000 and September 2001. The study was reported as a randomized, double-blind, active-controlled, non-inferiority study. The primary statistical evaluation focused on the two-sided 95% confidence interval on the difference in proportion of patients attaining clinical success at follow up. The analysis defined a delta of 0.1 as the appropriate non-inferiority margin.

[redacted]

1 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical- 2

2. Indications

2.1 Impetigo (NDA 22-055)

2.1.1 Study Designs

The Applicant provided data from two studies (TOC 103469 and TOC 100224) to support approval of this indication. These studies were conducted at study centers outside of the United States and were not conducted under the U.S. IND for retapamulin ointment. The studies were very similar in design with a few exceptions, which will be noted as appropriate in the following discussion. Study TOC 103469 was a multicenter, randomized, double-blind study comparing retapamulin to placebo (retapamulin or placebo ointment BID for 5 days) in the treatment of impetigo in patients >= 9 months old to adults. Study TOC 100224 was a multicenter, randomized, single-blind study comparing retapamulin to sodium fusidate ointment (retapamulin ointment BID for 5 days, sodium fusidate ointment TID for 7 days) in the treatment of impetigo in patients >= 9 months old to adults. The studies were randomized two retapamulin ointment patients to one placebo or fusidate ointment patient.

Clinical Team Leader Comment: Optimally, study TOC 100224 would have been double blinded; however, such blinding would have been very difficult due to both differing administration schedules and durations of therapy of products.

In both studies, patients >= 9 months of age were eligible for enrollment if they had: 1) a clinical diagnosis of primary impetigo (bullous and non-bullous) defined as a lesion or a group of lesions characterized by red spots or blisters without crusts which later progress to lesions which ooze and form yellow or honey-colored crusts surrounded by an erythematous margin, 2) no more than 10 discrete localized impetigo lesions suitable for topical treatment and the infected lesion(s) did not exceed 100 cm^2 in area with surrounding erythema not extending more than 2 cm from the edge of any lesion or up to a maximum of 2% body surface area for subjects <18 years of age, and 3) a total Skin Infection Rating Score (SIRS) of at least 8 (signs/symptoms included were: exudate/pus, crusting, erythema, tissue warmth, tissue edema, itching and pain – each of the components scored 0 to 6). Patients were excluded from the study if they had 1) an underlying skin disease (e.g., pre-existing eczematous dermatitis) or skin trauma, with clinical evidence of secondary infection, 2) signs and symptoms of systemic infection (such as fever; defined as an oral temperature greater than 101°F or 38.3°C), 3) a bacterial skin infection, which due to depth or severity, in the opinion of the investigator, could not be appropriately treated by a topical antibiotic (e.g., extensive cellulitis, furunculosis and abscess), or 4) received a systemic antibacterial, steroid, or had applied any topical therapeutic agent (including glucocorticoid steroids, antibacterials and antifungals) directly to the impetigo lesion(s), less than 24 hours prior to study entry.

Clinical Team Leader Comment: The inclusion and exclusion criteria used in the protocols were generally consistent with criteria recommended in the draft FDA Guidance for the uSSSI indication. While use of SIRS scores to determine

enrollment eligibility is subject to investigator interpretation, it did incorporate a measure of those signs and symptoms that are universally held to be the cardinal signs and symptoms of infection (i.e., dolor, rubor, fevor). Although curettage and needle aspirate would have been preferred methods for microbiologic sampling (protocols collected swab specimens), the specificity of the acute bacterial infection diagnosis was also further enhanced by use of microbiologic sampling of lesions to identify patients in whom a pathogen was present. Therefore, I consider the inclusion criteria used in the protocols to be adequate for this indication.

The test subjects or their caretakers were instructed in the proper technique for cleaning the wound and in the proper technique to apply the topical medication using a sterile swab. Use of dressings was permitted and the type of dressing used was recorded in the CRF as "occlusive", "semi-occlusive" or "none". In study TOC 103469, patient evaluations were made at: baseline (pre-therapy), optionally on day 3-4 of therapy (an on therapy visit), on day 7 (2 days post the end of retapamulin or placebo therapy, the end of therapy visit), and day 14 (follow-up visit). In study TOC 100224, patient evaluations were made at: baseline (pre-therapy), optionally on day 3-4 of therapy (an on therapy visit), on day 7 (2 days post the end of retapamulin therapy, the retapamulin end of therapy visit), on day 9 (2 days post end of fusidate therapy, the fusidate end of therapy visit) and day 14 (follow-up visit for both treatment groups). [The day 7 and day 9 visits were compared as the end of treatment visits for analyses of study TOC 100224.]

The Applicant's primary endpoint in study TOC 103469 was clinical outcome at end of therapy (EOT) in the clinical intent-to-treat population (ITTC). Key secondary efficacy endpoints included: 1) clinical response at EOT in PPC (clinical per protocol population), PPB (per protocol bacteriological population), and ITTB (bacteriological intent-to-treat population), 2) clinical response at follow-up (FU) in the ITTC, PPC, ITTB, and PPB, 3) microbiological response at EOT in the ITTB and PPB, 4) microbiological response at FU in the ITTB and PPB, and 5) the number and percent of subjects who had various pathogens including methicillin resistant *Staphylococcus aureus* (MRSA), mupirocin-resistant *Staphylococcus aureus* (mupRSA), and fusidic acid resistant *Staphylococcus aureus* (fusRSA) isolated at baseline, by clinical response at the EOT and FU.

In study TOC 100224, the Applicant's primary endpoint was clinical outcome at EOT in the clinical per protocol population (PPC). Key secondary endpoints included: 1) clinical response at Day 7 (2 days post therapy for retapamulin ointment and on-therapy for 2% sodium fusidate ointment), 2) clinical response at Day 9 (4 days after treatment for retapamulin ointment and 2 days after treatment for 2% sodium fusidate ointment), 3) clinical response at FU (Day 14 both treatment groups), 4) microbiological response at EOT in the ITTB and PPB, 5) microbiological response at FU in the ITTB and PPB, and 6) number and percent of subjects who had methicillin resistant *Staphylococcus aureus* (MRSA) isolated at baseline, by clinical response, at the EOT and FU.

Clinical Team Leader Comment: At the pre-NDA meeting the Applicant was informed that the Agency would consider clinical outcome at the FU visit as the primary endpoint in our assessment of efficacy for both studies.

A patient was included in the PPC if they "satisfy the inclusion/exclusion criteria and (who) subsequently adhere to the protocol." A patient was included in the PPB if they met criteria for the PPC and had a pathogen isolated from a specimen collected not more than 48 hours prior to beginning therapy.

In both studies clinical success at EOT was defined as "total absence of the treated lesions or the treated lesions have become dry without crusts compared to baseline, or improvement defined as a decline in the size of the affected area, number of lesions or both) such that no further antimicrobial therapy is necessary." At FU clinical success was defined as "continued absence of the treated lesions, or treated lesions have become dry without crusts with or without erythema compared to baseline, or improvement defined as a decline in the size of the affected area, number of lesions or both) such that no further antimicrobial therapy is required." A bacteriologic outcome of success was defined as eradication of baseline pathogen on culture obtained at the EOT visit or was presumed if the patient was a clinical success at the EOT visit and wounds were healed to the extent that no material was available to send for culture. At FU a bacteriologic outcome of success was defined as continued eradication of baseline pathogen on culture or continued presumed eradication in patients that had resolution of lesions such that no material was available to be cultured.

Study TOC 103469 was a superiority study, designed with 90% power and a one-sided alpha of 2.5%. A conclusion of superiority for retapamulin was to be drawn if the lower limit of the 95% confidence interval for the treatment difference was greater than zero.

Study TOC 100224, was a non-inferiority study designed with 90% power, a non-inferiority margin of 10% and a one-sided type 1 error rate of 2.5%. A conclusion of non-inferiority of retapamulin to fusidate was to be drawn if the lower limit of the 95% confidence interval for the treatment difference was greater than or equal to -10%.

<u>Clinical Team Leader Comment</u>: At the pre-NDA meeting with the Applicant regarding submission of this NDA, the Agency explained to the Applicant that because fusidate ointment was not approved in the U.S., the Agency would not consider study TOC 100224 as a pivotal study for support of the impetigo indication.

[redacted], which includes discussion of an article by Koning related to the efficacy of fusidic acid for treatment of impetigo.[1] In the Koning study the clinical and bacteriologic efficacy of fusidic acid cream plus disinfection with povidone-iodine versus placebo cream plus disinfection with povidone-iodine (treatment up to 14 days) for treatment of impetigo was assessed in 184 children aged 0 to 12 years. The study was randomized and double-blinded. Patients were

[1] Koning S, van Suijlekom-Smit LWA, Nouwen JL, Verduin CM, Bernsen RMD, Oranje AP, Thomas S, van der Wouden JC. Fusidic acid cream in the treatment of impetigo in general practice: double blind randomised placebo controlled trial British Medical Journal 2002; 324: 1-5.

assessed at 7, 14, and 21 days. Clinical cure was defined as "the complete absence of lesions or the lesions having become dry and without crusts; remaining local redness of intact skin was acceptable." The results of the study are provided in the Table

Table 2 Clinical effect and bacterial cure (intention to treat analysis). Values are numbers (percentages)

	Fusidic acid cream (n=76)	Placebo cream (n=80)
One week		
Clinical effect:		
Cure	42/76 (55)	10/80 (13)
Improvement	25/76 (32)	37/80 (46)
Failure	9/76 (11)	33/80 (41)
Bacterial cure	63/69 (91)	23/72 (32)
Two weeks		
Clinical effect:		
Cure	53/72 (73)	46/77 (60)
Improvement	17/72 (23)	20/77 (26)
Failure	2/72 (3)	11/77 (14)
Bacterial cure	62/70 (89)	52/70 (74)
Four weeks		
Clinical effect:		
Cure	70/76 (92)	69/78 (88)
Improvement	5/76 (7)	7/78 (9)
Failure	1/76 (1)	2/78 (3)
Bacterial cure	71/75 (95)	70/75 (93)

copied from the article below. While clinical and bacteriologic efficacy in the fusidic acid treatment group diminished over time, the data suggest that treatment with fusidic acid improves early clinical and bacteriologic cure rates and support a conclusion that fusidic acid is an active antibacterial product.

Additional support for the antibacterial effectiveness of topical fusidic acid for the treatment of impetigo is summarized in the 2004 Cochrane review that assessed the effects of treatments for impetigo.[2] Based on a systematic review of the literature, inclusive of placebo controlled trials in which topical fusidic acid was investigated, the authors concluded that there is good evidence that topical fusidic acid is equally, or more effective than oral treatment for people with limited disease. In addition, authors concluded that fusidic acid and mupirocin are of similar efficacy.

[2] Koning S, Verhagen AP, van Suijlekom-Smit LW, Morris A, Butler CC, van der Wouden JC. Interventions for impetigo. Cochrane Database Syst Rev. 2004;(2):CD003261.

2.1.2 Results

TOC 103469

Treatment groups were well balanced for baseline demographic factors in this study. There was a higher rate of premature withdrawal from study therapy in the placebo group; however, these discontinuations were predominantly due to lack of efficacy and disease progression (see Table 1, below).

Table 1. Number (%) of Subjects Withdrawn from the Study, by Reason for Withdrawal Study TOC 103469 (ITTC Population)

Reason for Withdrawal	Treatment Group		
	SB-275833 N= 139	Placebo N= 71	Total N= 210
	n (%)	n (%)	n (%)
Completed Study	122 (88)	40 (56)	162 (77)
Prematurely Withdrawn	17 (12)	31 (44)	48 (23)
Lack of Efficacy	5 (4)	18 (25)	23 (11)
Disease progression	3 (2)	9 (13)	12 (6)
Lost to Follow-Up	5 (4)	3 (4)	8 (4)
Subject decided to withdraw from study	2 (1)	0	2 (<1)
AE	1 (< 1)	1 (1)	2 (<1)
Protocol violation	1 (< 1)	0	1 (< 1)

n = number with clinical success outcome, N = number in analysis population

For further details regarding baseline demographic factors, subject disposition and reasons for exclusion from per protocol populations, please see the Clinical Review by David Bostwick.

The following table describes the results for the primary efficacy parameter, clinical response, by analysis population, at both EOT (Applicant's primary analysis time point) and FU (FDA's primary analysis time point).

Table 2. Clinical Response at End of Therapy and at Follow-up by Analysis Population – Study TOC 103469

	Retapamulin		Placebo		Difference in Success Rates (%)	95 % CI (%)
	n/N	Success Rate (%)	n/N	Success Rate (%)		
End of Therapy						
PPC	111/124	89.5	33/62	53.2	36.3	(22.8, 49.8)
ITTC	119/139	85.6	37/71	52.1	33.5	(20.5, 46.5)
PPB	96/107	89.7	26/52	50.0	39.7	(25.0, 54.5)
ITTB	101/114	88.6	28/57	49.1	39.5	(25.2, 53.7)
Follow Up						
PPC	98/119	82.4	25/58	43.1	39.2	(24.8, 53.7)
ITTC	105/139	75.5	28/71	39.4	36.1	(22.7, 49.5)
PPB	86/102	84.3	18/48	37.5	46.8	(31.4, 62.2)
ITTB	91/114	79.8	19/57	33.3	46.5	(32.2, 60.8)

n = number with clinical success outcome, N = number in analysis population, PPC = Clinical Per Protocol Population, ITTC = Clinical Intent to Treat Population, PPB = Bacteriological Per Protocol Population, ITTB = Bacteriological Intent to Treat Population

Examinations of results across baseline demographic factors were consistent with results displayed in Table 2.

The following table describes the clinical success at end of therapy and follow-up by baseline pathogen.

Table 3. Clinical Response at End of Therapy and Follow-Up for Patients With *Staphylococcus aureus* and *Streptococcus pyogenes* at Baseline in the Clinical Intent to Treat Population (ITTC) – Study TOC 103469

Pathogen	Retapamulin		Placebo	
	n/N	Success Rate (%)	n/N	Success Rate (%)
End of Therapy				
Staphylococcus aureus (Methicillin-susceptible)	84/95	88.4	27/51	52.9
Streptococcus pyogenes	30/34	88.2	3/8	37.5
Follow Up				
Staphylococcus aureus (Methicillin-susceptible)	75/95	78.9	18/51	35.3
Streptococcus pyogenes	29/34	85.3	1/8	12.5

n = number with clinical success outcome, N = number in analysis population

Clinical Team Leader Comment: At both EOT and FU clinical efficacy with retapamulin ointment is superior to treatment with placebo ointment across all treatment populations. The magnitude of the treatment benefit of topical retapamulin ointment over placebo in this study is consistent with the magnitude of the treatment benefit of topical mupirocin over placebo that has been observed in previously conducted placebo controlled trials for treatment of impetigo [redacted]

Analyses by baseline pathogen also demonstrate the superiority of treatment with retapamulin ointment to placebo ointment. No patient had a baseline culture positive for MRSA in this study. *S. aureus* isolates were not assessed for the presence of the Panton-Valentine Leukocidin (PVL) gene in this study.

TOC 100224

Treatment groups were well balanced for baseline demographic factors in this study with the exception that the mean and median age was slightly younger in sodium fusidate treated patients (mean age: 14.4 years, median age: 7 years) versus retapamulin treated patients (mean age: 17.8 years, median age: 9 years). For further details regarding baseline demographic factors, subject disposition and reasons for exclusion from per protocol populations, please see the Clinical Review by David Bostwick.

The following table describes the results for the primary efficacy parameter, clinical response, by analysis population, at both EOT (Applicant's primary analysis time point) and FU (FDA's primary analysis time point).

Table 4. Clinical Response at End of Therapy and at Follow-up by Analysis Population – Study TOC 100224

	Retapamulin		Sodium Fusidate		Difference in Success Rates (%)	95 % CI (%)
	n/N	Success Rate (%)	n/N	Success Rate (%)		
End of Therapy						
PPC	314/317	99.1	141/150	94.0	5.1	(1.1, 9.0)
ITTC	327/345	94.8	155/172	90.1	4.7	(-0.4, 9.7)
PPB	240/242	99.2	106/114	93.0	6.2	(0.5, 12.6)
ITTB	250/263	95.1	116/131	88.5	6.5	(1.4, 11.0)
Follow Up						
PPC	297/308	96.4	134/143	93.7	2.7	(-1.8, 7.2)
ITTC	310/345	89.9	150/172	87.2	2.6	(-3.3, 8.6)
PPB	227/235	96.6	99/107	92.5	4.1	(-1.4, 9.6)
ITTB	237/263	90.1	111.131	84.7	5.4	(-1.8, 12.5)

n = number with clinical success outcome, N = number in analysis population, PPC = Clinical Per Protocol Population, ITTC = Clinical Intent to Treat Population, PPB = Bacteriological Per Protocol Population, ITTB = Bacteriological Intent to Treat Population

Examinations of results across baseline demographic factors were consistent with results displayed in Table 4.

The following table describes the clinical success at end of therapy and follow-up by baseline pathogen.

Table 5. Clinical Response at End of Therapy and Follow-Up for Patients With *Staphylococcus aureus* and *Streptococcus pyogenes* at Baseline in the Clinical Per Protocol Population (PPC) – Study TOC 100224

Pathogen	Retapamulin		Sodium Fusidate	
	n/N	Success Rate (%)	n/N	Success Rate (%)
End of Therapy				
Staphylococcus aureus	209/211	99.1	90/97	92.8
Methicillin-susceptible	201/203	99.0	88/95	92.6
Methicillin-resistant	8/8	100	2/2	100
Streptococcus pyogenes	90/92	97.8	32/36	88.9
Follow Up				
Staphylococcus aureus	199/206	96.6	83/90	93.3
Methicillin-susceptible	191/198	96.5	81/88	92.0
Methicillin-resistant	8/8	100	2/2	100
Streptococcus pyogenes	87/91	95.6	31/36	86.1

n = number with clinical success outcome, N = number in analysis population

Clinical Team Leader Comment: Sodium fusidate ointment is not approved in the United States and from a regulatory perspective substantial evidence of efficacy and safety for sodium fusidate ointment to treat impetigo has not been established. Establishment of the non-inferiority of retapamulin ointment to sodium fusidate alone (by any delta margin), therefore, does not provide substantial evidence of effectiveness for retapamulin. Sodium fusidate is, however, an active antibacterial (see discussion in Clinical Team Leader Comment related to the description of this study design). Therefore, I consider analyses in which the point estimates for clinical and bacteriological efficacy of retapamulin ointment to be consistently 2% to 6% greater than those of sodium fusidate (statistically superior in three of four population analyses at EOT) to be compelling evidence of the antibacterial effectiveness of retapamulin ointment.

Only four of the MRSA isolates in this study contained the PVL gene, all cases were clinical successes. As in study TOC 103469, PVL gene status was not assessed in MSSA isolates.

2.1.3 Conclusion

The Applicant has provided substantial evidence of efficacy to support the conclusion that topical retapamulin ointment, 1% applied BID for five days is effective for the treatment of impetigo due to methicillin susceptible *S. aureus* and *S. pyogenes* in patients >= 9 months of age.

Evidence of efficacy is primarily provided by results of pivotal study TOC 103468 in which the clinical and bacteriological superiority of retapamulin ointment over placebo ointment was unequivocally demonstrated across all analysis populations at both end of therapy and follow-up assessments. Additional supportive evidence of efficacy is derived

from *in vitro* evidence of the antibacterial effectiveness of retapamulin (see FDA Microbiology Reviews by Avery Goodwin, Ph.D for NDA 22-055 [redacted]) and results of TOC 100224 in which the point estimates for clinical and bacteriological efficacy of retapamulin ointment were demonstrated to be consistently 2% to 6% greater than those of sodium fusidate (statistically superior in three of four population analyses at EOT).

[redacted]

[redacted]

[redacted]

2 Page(s) Withheld

X Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical- 3

[redacted]

[redacted]

2.2.4 Conclusion

[redacted]

2,

[redacted]

The Applicant has now provided substantial evidence of effectiveness of retapamulin ointment, 1% for the treatment of a closely related skin infection, impetigo, in NDA 22-055 and NDA 22-055 should be approved (see Section 2.1 above). [redacted]

3. Safety

For full discussion of safety findings please see the Clinical Reviews for [redacted] 22-055 conducted by David Bostwick. Primary safety issues related to use of topical retapamulin ointment, 1% are those related to dermatologic AEs at application site (e.g., irritation, erythema, etc.) and, as for all products, the potential for allergic reactions due to product components.

4. Recommendation on Approval

Retapamulin ointment, 1% (ALTABAX) may be approved for the indication: [redacted] Impetigo, [redacted] due to *Staphylococcus aureus* (methicillin susceptible) and *Streptococcus pyogenes* in patients >= 9 months of age.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jean Mulinde
4/6/2007 08:54:16 AM
MEDICAL OFFICER

Jean Mulinde
4/6/2007 08:56:00 AM
MEDICAL OFFICER

Janice Soreth
4/11/2007 06:16:54 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-055
Submission Code	N-000
Letter Date	June 12, 2006
Stamp Date	June 12, 2006
PDUFA Goal Date	April 12, 2007
Reviewer Name	David Bostwick
Review Completion Date	January 24, 2007
Established Name	Retapamulin Ointment, 1%
Trade Name	Altabax
Therapeutic Class	Topical anti-infective
Applicant	Glaxo Smith Kline
Priority Designation	S
Formulation	Ointment
Dosing Regimen	Topical, BID for 5 days
Indication	Treatment of impetigo
Intended Population	Pediatric $\geq$ 9 months of age and adult patients

Table of Contents

Appears This Way
On Original

1. EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

From a clinical perspective, this application may be approved for the indication treatment of impetigo up to 100 cm^2 in total area (up to 10 lesions). [redacted]

The Applicant has provided data that support the effectiveness and safety of this product when used on relatively small areas of impetigo due to *Staphylococcus aureus* (methicillin – susceptible isolates only) or *Streptococcus pyogenes*.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No post-marketing risk management activities other than routine surveillance are indicated.

1.2.2 Required Phase 4 Four Commitments

From a clinical standpoint, no Phase 4 commitments are indicated.

1.2.3 Other Phase 4 Requests

From a clinical standpoint, no Phase 4 requests are indicated.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical program

Altabax Ointment contains 1% retapamulin, a semisynthetic pleuromutilin antibiotic. In this review the terms "Altabax", "retapamulin", and "SB-275833" are interchangeable.

Two efficacy trials were submitted in support of the impetigo indication. The first, TOC 103409, was a superiority study comparing the efficacy and safety of Altabax Ointment to placebo. The study was performed in four overseas countries. The study enrolled 139 Altabax patients and 71 placebo patients for a total of 210 ITT patients. For reasons stated below, this is the sole acceptable pivotal study for impetigo. The study was randomized and double-blind.

The second study, TOC 100224, was a randomized, single-blind noninferiority study which compared BID treatment for 5 days with Altabax to TID treatment for 7 days with sodium fusidate ointment. Because sodium fusidate ointment has not been approved in the U.S., the reviewer must regard it as a placebo, since its activity against impetigo has not been evaluated in this country. Since Altabax failed to demonstrate superiority in this study, it is not acceptable as a pivotal study in support of the indication, though it is acceptable as a well-performed supportive study. The study was performed in nine overseas countries. The study enrolled 345 Altabax patients and 172 sodium fusidate patients for a total of 517 ITT patients.

The safety population consists of 484 Altabax patients, 71 placebo patients, and 172 sodium fusidate patients.

1.3.2 Efficacy

Protocol TOC 103469 is the sole pivotal efficacy study found acceptable in this application. It was a double-blind, randomized comparison of Altabax to its vehicle. The intent of the study was to establish that Altabax is superior to its vehicle in the treatment of impetigo when used BID for 5 days.

The study was successful in that Altabax was superior to placebo at the test of cure visit (follow-up, day 14 of the study) preferred by the reviewer. The sponsor test of cure visit was at end of therapy (day 7). Altabax was also superior to placebo at end of therapy. Other endpoints included microbiological response at follow-up and end of therapy and results for selected pathogens.

The following table presents the results for the primary efficacy outcome by analysis population. The ITT (ITTC), per protocol (PPC), ITT microbiological (ITTB) and per protocol microbiological (PPB) rates are given.

Table 1. Clinical Response at Follow-up by Analysis Population, Study TOC 103469

Analysis Population	SB-275833		Placebo		Difference in Success Rates (%)	95 % CI[2] (%)
	n/N[1]	Success Rate (%)	n/N[1]	Success Rate (%)		
ITTC	105/139	75.5	28/71	39.4	36.1	(22.7, 49.5)
PPC	98/119	82.4	25/58	43.1	39.2	(24.8, 53.7)
ITTB	91/114	79.8	19/57	33.3	46.5	(32.2, 60.8)
PPB	86/102	84.3	18/48	37.5	46.8	(31.4, 62.2)

1. n/N = number of successes/number of subjects that qualified for the respective analysis population in the respective treatment.
2. Confidence intervals were not adjusted for multiplicity.

Protocol TOC100224 is the other efficacy study submitted in support of the application. It was a single-blind (observer-blinded), randomized comparison of Altabax to sodium fusidate ointment 1%. Sodium fusidate ointment is approved for the treatment of impetigo in many foreign countries, but not in the U.S. The intent of the study was to establish that Altabax is not inferior to sodium fusidate ointment when Altabax is used BID for 5 days and sodium fusidate is used TID for 7 days.

The following table presents the results for the primary efficacy outcome, clinical response at follow-up, by analysis population.

Table 2. Clinical Response at Follow-up by Analysis Population, Study TOC 100224

Analysis Population	SB-275833		Sodium Fusidate		Difference in Success Rates (%)	95% CI (%)[1]
	n/N	Success Rate (%)	n/N	Success Rate (%)		
ITTC	310/345	89.9	150/172	87.2	2.6	(-3.3, 8.6)
PPC	297/308	96.4	134/143	93.7	2.7	(-1.8, 7.2)
ITTB	237/263	90.1	111/131	84.7	5.4	(-1.8, 12.5)
PPB	227/235	96.6	99/107	92.5	4.1	(-1.4, 9.6)

1. Confidence intervals were not adjusted for multiplicity

The following tables present the microbiological and clinical success rates for the pathogens sought in the labeling.

Table 3. Clinical Success Rate at Follow-up by Baseline Pathogen (PPC Population), Study TOC 103469

Pathogen[1]	SB-275833		Placebo		Difference in Success Rates (%)
	n/N[2]	Success Rate (%)	n/N[2]	Success Rate (%)	
S. aureus (all)	70/84	83.3	17/44	38.6	44.7
S. pyogenes	28/32	87.5	1/6	16.7	70.8
Other Strep. sp.	2/2	100	0	0	-
Other Gram (+)	1/1	100	0	0	-
Other Gram (-)	8/11	72.7	1/5	20	52.7
All pathogens	109/130	83.8	19/55	34.5	49.3
No pathogens	12/17	70.6	7/10	70	0.6

1. Individual pathogens not identified in 20 or more subjects were grouped
2. n/N = number of clinical success/number of pathogens present at baseline

Table 4. Clinical Success Rate at Follow-up by Baseline Pathogen (PPC Population), Study 100224

Pathogen[1]	SB-275833		Sodium Fusidate		Difference in Success Rates (%)
	n/N[2]	Success Rate (%)	n/N[2]	Success Rate (%)	
S. aureus (all)	199/206	96.6	83/90	92.2	4.4
MRSA[3]	8/8	100	2/2	100	0
MSSA[3]	191/198	96.5	81/88	92.0	4.4
S. pyogenes	87/91	95.6	31/36	86.1	9.5
Other Strep. sp.	4/4	100	3/3	100	0
Other Gram (+)	3/3	100	1/1	100	0
Other Gram (-)	12/14	85.7	14/16	87.5	-1.8
All pathogens	305/318	95.9	132/146	90.4	5.5
No pathogens	70/73	95.9	35/36	97.2	-1.3

1. Individual pathogens not identified in 20 or more subjects were grouped
2. n/N = number of clinical success/number of pathogens present at baseline
3. MRSA/MSSA are methicillin resistant/ susceptible *S. aureus* as defined by susceptibility to oxacillin.

These results require comment, as follows:

1. The reviewer considers Study TOC 103469 to be adequate evidence of the effectiveness of Altabax in the treatment of impetigo when used BID for 5 days. In all patient cohorts, the success rate for Altabax was at least 33% higher than for placebo. (A success was defined as absence of lesions, or dry, uncrusted lesions with or without erythema, or improvement such that no further antimicrobial therapy was required). While the study was relatively small, the results are statistically robust.

2. The results in the Altabax cohorts in the two efficacy studies are striking. When used in a similar manner in relatively similar patient populations, the success rate for Altabax in the placebo controlled study in the per protocol patients was 14% lower than in the sodium fusidate controlled study. In the ITT population, this difference was 14.5 %.

   While there may be a number of explanations for this difference, the most likely is the structure of the studies. It may be that superiority studies, such as the placebo controlled study reviewed here, encourage more critical patient evaluations than do non-inferiority studies because the evaluator is aware that all patients are not expected to improve equally.

3. Studies in the pediatric population were limited to children 9 months of age and older. It is logical to assume that younger children will be treated with the product, and safety and efficacy information in these smaller babies does not exist. [redacted] . A study in

pediatric patients aged 2 to 9 months is needed to achieve compliance with the Pediatric Research Equity Act. This study will include impetigo patients.

4. Impetigo is occasionally self-limiting, as seen by the 30 – 40% success rates for the placebo group in Study TOC103469. Especially in the context of a controlled clinical study, the concomitant care the patient receives may be more efficacious than would be given if the patient were not in the study. In this case, the patients were instructed in the proper techniques for cleansing the treatment area prior to drug application (twice daily). It is reasonable to assume that the cleansing alone would have a positive effect. Thus, the clinical benefit seen in these studies may not be duplicated in practice in the general patient population. Also, many of the lesions treated in these studies may not have required antimicrobial treatment prior to resolution if kept clean.

5. The studies submitted in support of this NDA were performed overseas. Adverse event reports are typically fewer in foreign based studies than in the U.S. As an example, adverse event reports were seen at about twice the frequency in the U.S. patients vs. foreign patients in the pivotal studies for [redacted]. Thus, the safety data reported here may not reflect the rate of adverse events which would be seen in the U.S. population. With these limitations in mind, the reviewer finds that safety and effectiveness for Altabax have been established for impetigo as described elsewhere in this review.

The following table lists the efficacy studies which were performed in support of this NDA.

Table 5. Table of Efficacy Studies

Protocol No.	**Type of Study**	**Study Objectives**	**Study Design**	**Key Inclusion Criteria**	**Test Drugs, Dosing Regimens and No. Enrolled**
TOC 103469	Phase 3 efficacy and safety	Evaluation of patients with impetigo	Randomized, double-blind, multi-center, superiority	Subjects ≥ 9 months old with impetigo	Altabax 139, Placebo, 71; BID for 5 days
TOC 100224	Phase 3 efficacy and safety	Evaluation of patients with impetigo	Randomized, evaluator-blind, multi-center, non-inferiority	Subjects ≥ 9 months old with impetigo	Altabax 345 BID for 5 days; Sodium fusidate 172 TID for 7 days

1.3.3 Safety

Safety for the use of Altabax in impetigo is supported by the adverse event reports seen in the Phase 3 studies. In the two impetigo studies combined, 484 subjects were exposed to Altabax Ointment, 71 to placebo and 172 to sodium fusidate. Exposure to Altabax and placebo was limited to 5 days, while sodium fusidate patients were exposed for 7 days.

The rate of drug related adverse events in the Altabax patients was 5%, which is consistent with the rate seen in the combined pivotal studies for [redacted]. There was only one drug-related adverse event (<1%) in the sodium fusidate cohort, while the rate in the placebo cohort was 3%. The most common adverse events, whether drug-related or not, seen in the Altabax patients were application site pruritus (3%) and headache and application site irritation (2% each). The most common adverse events in the sodium fusidate cohort were excoriation and urinary tract infection (2% each). The most frequent adverse events seen in the placebo group were impetigo exacerbation and xerosis (3% each). There were 3 (<1%) serious adverse events in the Altabax patients. None of them was considered to be drug-related by the investigators, though one (worsening of impetigo) could be related to lack of drug effect.

Other safety information (irritation, sensitization. absorption, QT effects) is referred to [redacted].

1.3.4 Dosing Regimen and Administration

The dosing regimen proposed here (BID for 5 days) is identical to that proposed for [redacted]. Altabax is effective in the treatment of impetigo using this dosing regimen.

1.3.5 Drug-Drug Interactions

No new information has been obtained related to drug- drug interaction. [redacted]

1.3.6 Special Populations

No new information has been obtained in special populations. It is noted that because impetigo is primarily a childhood disease, the patient population in this NDA is relatively young (the mean age of the Altabax patients in the placebo-controlled study is 12 years). With the exception of the additional pediatric data to be submitted, there are no issues remaining concerning special populations.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

2.1.1 Description of the Product

The product is a topical ointment containing 1 % retapamulin in white petrolatum.

2.1.2 Established Drug Name and Proposed Trade Name

Altabax (retapamulin ointment) Ointment 1%.

2.1.3 Clinical Class

Retapamulin is a semi-synthetic pleuromutilin antibiotic. It was first proposed for human use under [redacted]

2.1.4 Pharmacological Class

This product is a topical anti-infective.

2.1.5 Proposed Indications, Dosing Regimen, Age Groups

The product is proposed for use in patients with impetigo up to 100 cm^2 in total area (up to 10 lesions). The dosing regimen is twice daily for 5 days in patients 9 months of age and older.

2.2 Currently Available Treatment for Indications

Indications of this type are usually designated as part of the inclusive "uncomplicated skin and skin structure infections" (uSSSI) designation which is included in many systemic antibiotic labels. Examples include Cephalexin (1 to 4 g daily for adults; 25-50 mg/kg daily for pediatric patients), cefpodoxime proxetil (800 mg daily for patients 12 years and older), and azithromycin (500 mg on the first day followed by 250 mg daily in adults).

FDA's draft Guidance for uncomplicated SSSI recommends that 20% of the patients included in uSSSI studies intended to support NDA submission have a diagnosis of impetigo.

Bactroban (mupirocin) Ointment, 1 % (NDA 50-591) is the most commonly used topical medication for impetigo in the U.S.

2.3 Availability of Proposed Active Ingredient in the United States

Retapamulin is not available for human use in the U. S.

2.4 Important Issues With Pharmacologically Related Products

None. Two pleuromutilin antibiotics are available in the U.S. for veterinary use.

2.5 Presubmission Regulatory Activity

Most of the pre-submission regulatory activity for Altabax concerned [redacted]. The Applicant had originally informed FDA that they were not interested in marketing Altabax for impetigo in the U.S. but were interested in marketing the product overseas for impetigo. Early in 2006, they decided to apply for approval of the impetigo indication in this country. Since the clinical studies were already underway overseas, FDA had no input into the protocols for the pivotal studies. A pre-NDA meeting was held for the impetigo indication on May 8, 2006. The Applicant was informed at that meeting that the study comparing Altabax to sodium fusidate would not be acceptable as a pivotal study.

2.6 Other Relevant Background Information

[redacted]

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

No new information related to chemistry, manufacturing controls or product microbiology was included in this submission. [redacted]

3.2 Animal Pharmacology/Toxicology

No new information related to animal pharmacology/toxicology was included in this submission. [redacted]

3.3 Microbiology

This review is not yet available.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The trials submitted with the NDA (see following table) were the principal data source for this review.

4.2 Tables of Clinical Studies

Table 1. Table of Efficacy Studies

Protocol No.	Type of Study	Study Objectives	Study Research	Key Inclusion Criteria	Test Drugs, Dosage Regimens and No. Enrolled
TOC 103469	Phase 3 efficacy and safety	Evaluation of patients with impetigo	Randomized, double-blind, multicenter, superiority	Subjects ≥ 9 months old with impetigo	Altabax 139, Placebo 71; BID for 5 days
TOC 100224	Phase 3 efficacy and safety	Evaluation of patients with impetigo	Randomized, evaluator-blind, multicenter, non-inferiority	Subjects ≥ 9 months old with impetigo	Altabax 345, BID for 5 days; Sodium fusidate 172, TID for 7 days

4.3 Review Strategy

Data from the two studies listed above were reviewed. Literature was not used for safety or efficacy evaluations

4.4 Data Quality and Integrity

Division of Scientific Investigation audits have been requested for two of the foreign investigators. Preliminary results of these investigations indicate that there are no issues which would indicate that the results from the centers are not reliable. The reviewer also performed a blinded review of a random sample of 15% of the Case Report Forms (CRF's) from the placebo-

controlled clinical study. The error rate found was acceptable, and for the most part the results presented in this review are the same as those presented by the applicant. This CRF review is discussed in detail in section 6.1.4 below.

4.5 Compliance with Good Clinical Practices

The sponsor has provided statements that the studies were performed in compliance with good clinical practices. The protocol states that informed consent was to be obtained from all study participants or their legal guardian.

4.6 Financial Disclosures

Financial disclosure information is adequate. Four investigators did not provide financial disclosure information. All these investigators were attached to one test site in Canada. This site was involved in study TOC 100224, the non-inferiority study vs. sodium fusidate, and entered 2 evaluable patients.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

No new information is submitted in this NDA concerning pharmacokinetics. Please see Dr. Charles Bonapace's Clinical Pharmacology and Biopharmaceutics review dated March 8, 2007.

5.2 Pharmacodynamics

No new information is submitted in this NDA concerning pharmacodynamics relationships. Please see Dr. Bonapace's review in this regard.

5.3 Exposure-Response Relationships

No new information is submitted in this NDA concerning exposure-response relationships. Please see Dr. bonapace's review in this regard.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The indication being sought for this NDA is: [redacted] :

Altabax is indicated for the topical treatment of the following uncomplicated skin and skin structure infections (SSSI) due to *Staphylococcus aureus* (methicillin-susceptible isolates only) or *Streptococcus pyogenes*:

- Impetigo: up to 100 cm^2 in total area (up to 10 lesions)

6.1.1 Methods

Two pivotal studies were submitted in support of the impetigo indication : Study TOC 103469 was a multicenter, randomized, double-blind study comparing Altabax to placebo in the treatment of impetigo in patients ≥ 9 months old to adults; Study TOC 100224 was a multicenter, randomized, single-blind study comparing Altabax to sodium fusidate ointment in the treatment of impetigo in patients ≥ 9 months old to adults.

Reviewer's Comment: These studies were initiated and completed without submission to an IND (they were performed completely overseas). Therefore, FDA has had no opportunity to comment on the study protocols.

6.1.2 General Discussion of Endpoints

The endpoints used in this study are consistent with those used in previous applications with similar indications. Since an infective process is under evaluation, both clinical and microbiological endpoints are necessary.

The Applicant's preferred endpoint is clinical success at end of therapy. However, the Division has consistently used clinical success at the follow-up visit as the primary endpoint for studies of this type, and this is the primary endpoint for the purpose of this review. The definition of a clinical success at the follow-up was continued absence of the treated lesion, or the treated lesions had become dry without crusts with or without erythema compared to baseline, or improvement (defined as a decline in the size of the affected area, number of lesions or both) such that no further antimicrobial therapy was required. This is an admittedly imprecise evaluation which permits a wide range of responses from no symptomatology at follow-up to minimal improvement which in the investigator's estimation does not require further therapy.

The microbiological endpoint (conversion of pathogen) is much more specific, which is why it is necessary to include a significant number of microbiologically evaluable cases in the database.

The protocol also lists assessment of lesion area as a study endpoint, which is appropriate. However, the reviewer has the following comment concerning SIRS (sign and symptoms) scores.

Reviewer's Comment: A SIRS score of at least 8 was required for a subject to be included in the study. The SIRS score is arrived at by evaluating the signs /symptoms exudate/pus, crusting, erythema, tissue warmth, tissue edema, itching and pain on a scale from 0 = absent to 6 = severe. The scores from the individual signs and symptoms are totaled to

arrive at the SIRS score. The reviewer considers this evaluation to be a meaningful measure of the severity of the disease, and it is therefore included in the efficacy outcomes.

However, the Applicant states that the SIRS score was only included as an aid to investigators, and includes the following statement: "It is a non-validated tool and SIRS scores were not used to evaluate clinical outcome". This is difficult to reconcile with the sponsor's use of SIRS scores to assist in evaluating clinical outcome in very similar studies, and with the use of the SIRS score as an inclusion criterion for entering the clinical studies. In any event, the reviewer considers SIRS scores to be a useful tool.

Study TOC 103469 was adequately blinded (double-blind) comparison to placebo. The blinding of study TOC 100224 was less than ideal. Since the test products had different dosage regimens (Altabax BID for 5 days, sodium fusidate TID for 7 days), only the evaluator was blinded. This is not critical because the reviewer does not consider TOC 100224 to be an acceptable pivotal study, as the chosen comparator is not approved in the U. S.

6.1.3 Study Design

6.1.3.1 Overview

Reviewer's Note: There were two similar studies submitted in support of this NDA. Many of the protocol elements were identical or very similar in the studies, with the main difference being the choice of comparators. The following study design section concerns both studies. If no mention is made of Study TOC 100224 (the sodium fusidate controlled study), it should be presumed that the protocol element is the same as for Study TOC 103469 (the placebo controlled study), which is completely described below.

(Study TOC 103469). This was an outpatient study. The test subjects or their caretakers were instructed in how to apply the medication, including cleansing of the wound prior to medication application. Use of dressings was permitted and the dressing configuration was noted in the CRF. The medications were applied BID for 5 days. Patient evaluations were made at baseline. There was an optional interim visit at day 3-4 of therapy. The end of therapy visit was at day 7 (2 days after therapy stopped), and the followup visit was at day 14.

(Study TOC 100224). This was also an outpatient study. The test subjects or their caretakers were instructed in how to apply the medication, including cleaning the wound prior to application. Use of dressings was permitted and the dressing configuration was noted in the CRF. The dosing regimens differed as required by the labeling for sodium fusidate ointment. Altabax was applied BID for 5 days while sodium fusidate was applied TID for 7 days. Patient evaluations were made at baseline. There was an optional interim visit at day 3-4 of therapy. Visit 2 was at day 7, 2 days after treatment with Altabax stopped. Visit 3 was at day 9, 2 days after sodium fusidate treatment stopped. Visits 2 and 3 were the end of therapy visit. The followup visit (visit 4) was at day 14 for all patients.

6.1.3.2 Inclusion and Exclusion Criteria

(Study TOC 103469)

Inclusion criteria

A subject was eligible for inclusion in this study only if all of the following criteria applied:

1. The subject was ≥ 9 months of age (age ≥18 months of age for the Netherlands only).
2. The subject had a clinical diagnosis of primary impetigo (bullous and non-bullous) defined as a lesion or a group of lesions characterized by red spots or blisters without crusts which later progress to lesions which ooze and form yellow or honey-coloured crusts surrounded by an erythematous margin.
3. The subject had no more than 10 discrete localized impetigo lesions suitable for topical treatment.
4. The infected lesion(s) did not exceed 100cm² in area with surrounding erythema not extending more than 2 cm from the edge of any lesion or up to a maximum of 2% body surface area for subjects <18 years of age. If a subject had multiple lesions the total area did not exceed a total of 100cm².
5. The subject was of (a) non-childbearing potential (i.e. physiologically incapable of becoming pregnant [tubal ligation], including any female who was post-menopausal [>1 year without menstrual period], including any female who was pre-menarchal); or (b) childbearing potential or less than one year post-menopausal who had a negative urine pregnancy test prior to enrollment, and had agreed to complete abstinence from sexual intercourse, or was using an acceptable method of contraception during the study (i.e. surgical sterilization, intra-uterine device [IUD] with published data showing that the expected failure rate is less than 1% per year [not all IUDs meet this criterion], oral contraception plus barrier contraception, other hormone delivery systems plus barrier contraception, diaphragm or condom in combination with contraceptive cream, jelly or foam).
6. The subject had a Skin Infection Rating Scale (SIRS) Score of at least 8
7. The subject was willing and able to comply with the study protocol.
8. The subject had given written informed, dated consent to participate in the study.

A paediatric subject under the legal age of consent (dependent on local country practice) was included if the following applied:

1. The parent/legal guardian was willing to comply with the protocol.
2. The child had given their assent to participate in the study (this was only required if the child was of an age to assent to enroll in the study – the age of assent was determined by IRB/IEC or was consistent with local legal requirements).
3. The parent/legal guardian had given written informed, dated consent for the subject to participate in the study.

Exclusion criteria

A subject was not eligible for inclusion in this study if any of the following criteria applied:

1. The subject demonstrated a previous hypersensitivity reaction to SB-275833 or any component of the ointment (refer to the Investigator Brochure for composition of SB-275833 Ointment).

2. The subject had an underlying skin disease (e.g., pre-existing eczematous dermatitis) or skin trauma, with clinical evidence of secondary infection.

3. The subject had signs and symptoms of systemic infection (such as fever; defined as an oral temperature greater than 101°F or 38.3°C).

4. The subject had a bacterial skin infection, which due to depth or severity, in the opinion of the investigator, could not be appropriately treated by a topical antibiotic (e.g., extensive cellulitis, furunculosis and abscess).

5. The subject received a systemic antibacterial, steroid, or had applied any topical therapeutic agent (including glucocorticoid steroids, antibacterials and antifungals) directly to the impetigo lesion(s), less than 24 hours prior to study entry.

6. The subject had a serious underlying disease that could be imminently life threatening.

7. The subject was pregnant, breast-feeding or planning a pregnancy during the study.

8. The subject used an investigational drug within 30 days prior to entering the study.

9. The subject was previously enrolled in this study or in any other study involving SB-275833.

(Study TOC 100224)

Inclusion and exclusion criteria were the same as for Study 103469, with the exception that those patients who had previously exhibited hypersensitivity reactions to sodium fusidate ointment were also excluded.

6.1.3.3 Study Procedures

Study Treatments

(Study TOC 103469)

Patients were randomized 2 Altabax to 1 placebo and were treated BID for 5 days.

(Study TOC 100224)

Patients were randomized 2 Altabax to 1 sodium fusidate ointment. Altabax patients were treated BID for 5 days and sodium fusidate patients were treated TID for 7 days.

Blinding

(Study TOC 103469)

This was a double blind study.

(Study TOC 100224)

This was a single-blind (evaluator-blind) study.

Reviewer's Comment: It should be noted that the test preparations were different colors in study TOC 100224. At least at the end of therapy visit for Altabax (day 7), it seems likely that the observer could tell which medication was being used.

Choice of Control Group

(Study TOC 103469)

Placebo was used as the control and is appropriate.

(Study TOC 100224)

The sponsor chose sodium fusidate ointment because it is approved in many foreign countries for the treatment of impetigo.

Reviewer's Comment: Sodium fusidate has never been approved in the U.S. and thus is not an acceptable active control for use in a non-inferiority study submitted for approval by U. S. regulators.

Microbiological Methods

Bacteriological samples were taken from the primary lesion site using cotton swabs for cultures, Gram stain and susceptibility testing. At subsequent visits, bacteriological samples were only collected from patients who were clinical failures. For other subjects, bacteriological outcome was assessed according to clinical criteria.

Reviewer's Comment: The preference of the reviewer is for use of needle biopsy or curettage for microbiological sampling. Also, it is preferable to sample pus/exudate whenever it is noted. However, these studies were performed without FDA input.

Study Evaluations

(Study TOC 103469)

At baseline:
- Clinical assessment. Where subjects had multiple lesions, the most serious was made the primary lesion
- Medical history/ physical exam
- SIRS scale evaluation
- Microbiological sampling
- Lab testing (hematology, blood chemistries, urinalysis)
- Pregnancy testing

On therapy (failure or withdrawal only):
- Clinical assessment
- SIRS scale evaluation
- Microbiological sampling

End of therapy (day 7):
- Clinical assessment
- SIRS scale evaluation
- Blood and urine for lab testing
- Record type of dressing used
- If the patient is a failure, microbiological testing was to be performed

Follow-up (day 14):
- Same as end of therapy, with the exception that labs were not done

The following lab tests were run on the blood and urine samples taken at the end of therapy:

Hematology: hemoglobin, hematocrit, red cell count, platelet count, white cell count, differential white cell count (neutrophils, lymphocytes, monocytes, eosinophils, basophils).

Blood chemistries: alkaline phosphatase, aspartate transaminase (AST), alanine transaminase (ALT), blood urea nitrogen (BUN), gamma glutamyl transferase, albumin, total bilirubin, total protein, creatine kinase, lactate dehydrogenase, serum creatinine, uric acid, glucose, calcium, potassium and calculated creatinine clearance.

Urinalysis: blood, glucose, protein by dipstick and WBCs by microscopy.

Signs and Symptoms: The signs and symptoms of infection were evaluated using a Skin Infection Rating Scale (SIRS). The signs/symptoms included were: exudate/pus, crusting, erythema, tissue warmth, tissue edema, itching and pain. A score was assigned to each of the signs/symptoms and a total score calculated. The scoring scale is as follows:

0 = absent =	no evidence of the signs of symptoms
1	
2 = mild =	signs/symptoms are present but not intense
3	
4 = moderate =	signs/symptoms are clearly evident, intense, and are somewhat bothersome to the patient
5	
6 = severe =	signs/symptoms are clearly evident, intense, and extremely bothersome to the patient

The 1, 3, and 5 scores are half-scale evaluations with no written definition.

Wound size: The size of the lesion was measured at baseline and end of therapy.

(Study TOC 100224)

The study evaluations were the same as for Study 103469, above. However, it should be noted that the end of therapy visit was at day 7 for the Altabax patients and day 9 for the sodium fusidate patients (all patients were to be seen at both visits).

Safety Considerations

- Patients were examined for AE's at each visit. An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding) symptom or disease (new or exacerbated) temporally associated with the use of a medicinal product.
- A subject could withdraw from the study at any time at their own request, or the investigator could withdraw them. Reasons for withdrawal were documented.

6.1.3.4 Study Populations

The sponsor evaluated four subject populations as follows:

Intent to Treat Clinical (ITTC):	All randomized subjects who take at least one dose of coded study medication.
Bacteriology ITT (ITTB):	All randomized subjects who take at least one dose of coded study medication and documented evidence of a bacterial infection at baseline.
Clinical Per Protocol (PPC):	This population includes subjects who satisfy the inclusion/exclusion criteria and who subsequently adhere to the protocol. The clinical PP population is a subset of the clinical ITT population.
Bacteriology PP (PPB)	This population includes subjects who satisfy the inclusion/exclusion criteria, who subsequently adhere to the protocol, and who have documented evidence of a bacterial infection at baseline, from a specimen collected not more than 48 hours prior to beginning therapy. The bacteriology PP population is a subset of the bacteriology ITT population.

This was a superiority trial with 90% power and a one-sided type 1 error rate of 2.5%. All patients who took at least one dose of study medication were included in the study analysis.

6.1.3.5 Outcome Criteria

(Study TOC 103469)

1. Clinical: The reviewer's primary efficacy parameter was clinical response at follow-up. The investigator assigned one of the following outcomes for each patient:

Outcomes	Defining criteria	Clinical Response at Follow-up (Day 14)
Follow-up Clinical Success	Continued absence of the treated lesions, or treated lesions have become dry without crusts with or without erythema compared to baseline, or improvement (defined as a decline in the size of the affected area, number of lesions or both) such that no further antimicrobial therapy is required.	Clinical success
Clinical recurrence	Reappearance or worsening of lesions i.e increase in the number of lesions and/or lesion area for subjects who were clinical successes at the end of therapy.	Clinical failure
EOT Failure	The subject was an end of therapy failure. This outcome will be programmatically assessed by GlaxoSmithKline and not the investigator.	Clinical failure
Unable to determine	Refusal to consent to a clinical examination or lost to follow-up. Subjects who are 'unable to determine' at end of therapy are considered 'unable to determine' at follow-up as well.	Clinical failure

For purposes of data analysis the "Clinical recurrence" and "Unable to determine" categories were considered clinical failures.

The sponsor's primary efficacy parameter was clinical response at end of therapy. The investigator assigned one of the following outcomes for each patient at the end of therapy exam:

Outcomes	Defining criteria	Clinical Response At End of Therapy
Clinical Success	Total absence of the treated lesions or the treated lesions have become dry without crusts compared to baseline, or improvement (defined as a decline in the size of the affected area, number of lesions or both) such that no further antimicrobial therapy is necessary.	Clinical success

Clinical failure	Insufficient improvement or deterioration (i.e., lesions remain crusted and/or have exudate leaving a yellow or honey coloured crust, lesion area has increased with or without an increase in the number of lesions) compared to baseline such that additional antibiotic therapy is required. Subjects who are clinical failures at end of therapy are considered clinical failures at follow-up as well.	Clinical failure
Unable to determine	Refusal to consent to a clinical examination or lost to follow-up. Subjects who are 'unable to determine' at end of therapy are considered 'unable to determine' at follow-up as well.	Clinical failure

For purposes of data analysis, the "Clinical failure" and "Unable to determine" patients were considered clinical failures.

2. Microbiological: The following table describes the categories of microbiological response to be evaluated at the follow-up visit.

Table 2. Microbiological Outcomes at Follow-up

Defining criteria	**Outcome**	**Microbiological Response Follow-up (Day 14)**
For subjects whose clinical response at the end of therapy was 'clinical failure', and who do not have cultures obtained at follow-up		
Subject is a 'clinical failure' at end of therapy and no culture	Microbiological Presumed Persistence	*Microbiological Failure*
For subjects whose clinical response at end of therapy was 'clinical success'		
The baseline pathogen was eradicated or presumed eradicated at end of therapy and there was continued absence of the pathogen from a swab sample taken at the follow-up.	Follow-up Microbiological Eradication	*Microbiological Success*
The baseline pathogen was eradicated or presumed eradicated at end of therapy, subject is a follow-up clinical success, such that no culture was obtained due to lack of culturable material, secondary to adequate clinical response, and is documented in the eCRF.	Presumed Follow-Up Microbiological Eradication	*Microbiological Success*
Baseline pathogens(s) was present at end of therapy and is still present.	Microbiological Persistence	*Microbiological Failure*
The baseline pathogen was eradicated or presumed eradicated at end of therapy and reappears at follow-up.	Microbiological Recurrence	*Microbiological Failure*

The baseline pathogen was eradicated or presumed eradicated at end of therapy, no sample for culture is taken at the follow-up visit and subject is a clinical recurrence.	Microbiological Presumed Recurrence	*Microbiological Failure*
An assessment of bacteriological outcome could not be made at end of therapy or follow-up.	Unable to Determine	*Microbiological Failure*
New pathogens isolated at follow-up (i.e. not present at baseline or end of therapy) will be classified according to the following categories:		
A new pathogen, not previously identified at baseline or end of therapy, is identified at follow-up in a symptomatic subject requiring additional antibiotic therapy, i.e., subject is a clinical recurrence	New Infection	*Microbiological Failure*
A new pathogen, not previously identified at baseline or end therapy, is identified at follow-up in a non-symptomatic subject who does not require additional antibiotic therapy, i.e., subject is a follow-up clinical success.	Colonisation	*Microbiological Success*
NB: For those subjects withdrawing prior to the end of therapy visit, evaluation of their by pathogen and by subject microbiological response will be determined at the time they are withdrawn.		

(Study TOC 100224)

The outcome criteria were the same as for Study 103469, above. Since the Altabax patients had an end of therapy visit at day 7 and an additional evaluation at day 9, these patients could only be a clinical success at follow-up if they were clinical successes at both day 7 and 9.

6.1.3.6 Statistical Plans

(Study TOC 103469)

This was a superiority study, with 90% power and a one-sided alpha of 2.5%. A conclusion of superiority for Altabax was to be drawn if the lower limit of the 95% confidence interval for the treatment difference was greater than zero.

(Study TOC 100224)

This was a non-inferiority study with 90% power, a non-inferiority margin of 10% and a one-sided type 1 error rate of 2.5%. A conclusion of non-inferiority of Altabax to fusidic acid was to be drawn if the lower limit of the 95% confidence interval for the treatment difference was greater than or equal to -10%.

6.1.4 Efficacy Findings

6.1.4.1 Study TOC 103469

1. Disposition of subjects: A total of 213 subjects were randomized into the study at a rate of 2 Altabax to 1 placebo. The following table presents the disposition of these subjects.

Table 3. Subject Disposition

Subject Disposition	Treatment		Total
	SB-275833	Placebo	
Randomized	140	73	213
Randomized but not treated	1	2	3
Completed Study	122	40	162

The following table presents the reasons for early withdrawal from the study.

Table 4. Number (%) of Subjects Withdrawn from the Study, by Reason for Withdrawal (ITTC Population)

Reason for Withdrawal	Treatment Group		
	SB-275833 N= 139	Placebo N= 71	Total N= 210
	n (%)	n (%)	n (%)
Completed Study	122 (88)	40 (56)	162 (77)
Prematurely Withdrawn	17 (12)	31 (44)	48 (23)
Lack of Efficacy	5 (4)	18 (25)	23 (11)
Disease progression	3 (2)	9 (13)	12 (6)
Lost to Follow-Up	5 (4)	3 (4)	8 (4)
Subject decided to withdraw from study	2 (1)	0	2 (<1)
AE	1 (< 1)	1 (1)	2 (<1)
Protocol violation	1 (< 1)	0	1 (< 1)

Reviewer's Comment: The high number of withdrawals in the placebo group was mostly due to lack of effectiveness. The discontinuances due to adverse events will be discussed in the safety section below.

The following table summarizes the number of patients analyzed in the various cohorts. Please note that Table 4 above only concerns withdrawals so the total that completed the study is not the same as the per protocol total.

Table 5. Summary of Analysis Populations

Analysis Population	SB-275833 (N = 139)	Placebo (N = 71)	Total (N = 210)
Intent-to-Treat Clinical Population	139 (100.0%)	71 (100.0%)	210 (100.0%)
Per Protocol Clinical	119 (85.6%)	58 (81.7%)	177 (84.3%)
Reason for PP Exclusion			
Inclusion or exclusion criteria not met	2 (1.4%)	0 (0.0%)	2 (1.0%)
Did not return for scheduled FU visit	2 (1.4%)	2 (2.8%)	4 (1.9%)
Was exposed to other topical treatment	7 (5.0%)	7 (9.9%)	14 (6.7%)
Relative day is not in a specified visit window	6 (4.3%)	4 (5.6%)	10 (4.8%)
Clinical response was UTD[1]	7 (5.0%)	6 (8.5%)	13 (6.2%)
Intent-to Treat Bacteriological Population	114 (82.0%)	57 (80.3%)	171 (81.4%)
Reason for ITTB Exclusion			
Isolate not sent to central laboratory	1 (0.7%)	0 (0.0%)	1 (0.5%)
No Baseline Pathogen Isolated	24 (17.3%)	14 (19.7%)	38 (18.1%)
Per Protocol Bacteriological[2]	102 (73.4%)	48 (67.6%)	150 (71.4%)
Reason for PPB Exclusion			
Inclusion or exclusion criteria not met	1 (0.7%)	0 (0.0%)	1 (0.5%)
Did not return for scheduled FU visit	2 (1.4%)	2 (2.8%)	4 (1.9%)
Was exposed to other topical treatment	3 (1.4%)	4 (5.6%)	7 (3.3%)
Relative day is not in a specified visit window	5 (3.6%)	3 (4.2%)	8 (3.8%)
Clinical response was UTD[1]	4 (2.9%)	4 (5.6%)	8 (3.8%)

(1) UTD = Unable to Determine
(2) Subjects in the PPB population are those from the ITTB population without protocol violations

2. Investigators: This was a multi-center study conducted at 17 independent sites in 4 countries under a common protocol. There were 11 sites in the Netherlands and 2 each in Mexico, Peru and India. The following presentation lists the principal clinical investigators and the sponsor's intent-to-treat patient population enrollment by investigator. The presentation also lists the number of patients who were clinically and microbiologically evaluable. The table does not list investigators who had no evaluable patients.

The percentages in the following table represent the following:

- The percentage figure following the ITT number is the proportion of the total ITT population enrolled by that investigator.

- The percentage following the clinically and microbiologically evaluable numbers are the proportions of the patients evaluable for that cohort by center, based on the ITT population for that investigator.

Table 6. Subject Accountability by Investigator

Study Center/ Investigator/ Location	ITT Analysis (n) (% of total ITT population)	Clinically Evaluable (n) (% of Center population)	Micro Evaluable (n) (% of Center population)
[redacted] Roelofarendoseen, Netherlands	3 (1.4)	3 (100)	2 (66)
[redacted] Musselkanaal, Netherlands	4 (1.9)	3 (75)	3 (75)
[redacted] Woerden, Netherlands	4 (1.9)	4 (100)	4 (100)
[redacted] Rotterdam, Netherlands	8 (3.8)	5 (63)	4 (50)
[redacted] Deurne, Netherlands	6 (2.8)	5 (83)	4 (66)
[redacted] Beeken Donk, Netherlands	2 (1.0)	2 (100)	2 (100)
[redacted] Ermelo, Netherlands	4 (1.9)	4 (100)	4 (100)
[redacted] Rotterdam, Netherlands	22 (10.4)	19 (86)	17 (77)
[redacted] Zwijndrecht, Netherlands	1 (0.5)	1 (100)	1 (100)
[redacted] Soerendonk, Netherlands	2 (1.0)	1 (50)	1 (50)
[redacted] Gouda, Netherlands	4 (1.9)	3 (75)	3 (75)
[redacted] Lima, Peru	19 (9.0)	18 (95)	16 (84)
[redacted] Jalisco, Mexico	25 (12.5)	17 (68)	16 (64)

[redacted] Andhra Pradesh, India	40 (19.0)	33 (83)	22 (55)
[redacted] Karnataka, India	48 (22.9)	43 (90)	37 (77)
[redacted] Callao, Peru	15 (7.1)	11 (73)	11 (73)
[redacted] Mexico City, Mexico	3 (1.4)	3 (100)	3 (100)

Reviewer's Comment: The two investigators from India enrolled about 42% of the ITT population.

3. Demographics: The following table provides the demographic characteristics of the ITT population by test cohort.

Table 7. Demographic Characteristics (ITTC Population)

Demographic Characteristic	Treatment Group		Total
	SB-275833 N = 139	Placebo N = 71	N=210
Age (yr)			
Mean (SD)	12.3 (14.0)	8.9 (8.9)	11.1 (12.6)
Median	8.0	7.0	7.0
Range	0 -73	0 -44	0-73
Gender, n (%)			
Female	73 (53)	34 (48)	107 (51)
Male	66 (47)	37 (52)	103 (49)
Race, n (%)			
African American/ African heritage	2 (1)	3 (4)	5 (2)
American Indian or Alaskan native	23 (17)	13 (18)	36 (17)
Asian - Central/ South Asian heritage	59 (42)	30 (42)	89 (42)
White - Arabic/ North African heritage	2 (1)	0	2 (1)
White - White/ Caucasian/ European heritage	52 (37)	23 (32)	75 (36)
Mixed Race	1 (<1)	2 (3)	3 (1)
Ethnicity, n (%)			
Hispanic/ Latino	39 (28)	23 (32)	62 (30)
Not Hispanic/ Latino	100 (72)	48 (68)	148 (70)
Age Strata			
9 months - <2 years	12	6	18
2 years - < 6 years	38	24	62
6 years - <13 years	56	28	84
13 years - < 18 years	5	6	11
18 years - <65 years	25	7	32
≥ 65 years	3	0	3

Reviewer's Comment: It is noted that the placebo patients were on average younger than the Altabax patients. Additionally, the 17% American Indian or Alaskan native figure is puzzling, though this may include patients from the South American investigators.

The following table presents the diagnosis (bullous vs. non-bullous impetigo) in the populations analyzed.

Table 8. Clinical Diagnosis of Impetigo at Baseline in Each Analysis Population

Demographic Characteristic	Treatment Group	
	SB-275833	Placebo
Bullous, n (%)		
ITTC	26 (18.7)	11 (15.5)
PPC	20 (16.8)	8 (13.8)
ITTB	19 (16.7)	8 (14.0)
PPB	15 (14.7)	6 (12.5)
Non-bullous, n (%)		
ITTC	113 (81.3)	60 (84.5)
PPC	99 (83.2)	50 (86.2)
ITTB	95 (83.3)	49 (86.0)
PPB	87 (85.3)	42 (87.5)

4 Effectiveness Parameters

Reviewer's Comments: The applicant's database was reviewed using a 15% random sample cohort. Variables analyzed included evaluability, outcome assignments and accuracy of data transportation to line listings. This review showed disagreement between the sponsor and reviewer in 2/32 (6%) of cases. In the first case, a placebo patient who was properly classified as a clinical failure was classified as a microbiological success, though no pathogen was listed at the baseline visit. In the second, an Altabax patient who was properly classified as a clinical failure and who had a pathogen identified at baseline had no microbiological outcome stated in the line listings. These errors would not impact the primary efficacy analysis. This error rate is satisfactory in that experience has demonstrated that such rates are unlikely to affect the outcome of studies of this size. Therefore, the results presented will be those submitted by the Applicant. An additional sensitivity analysis was performed by FDA personnel, and will be identified as such in the results.

Primary Efficacy Results- Clinical Response at Follow-up

The following table presents the success rates in the various defined populations at follow-up. This is the reviewer's primary efficacy outcome for this study. Two observations concerning these results are relevant:

i. "Success" was defined as an absence of treated lesions, improved lesions with or without erythema, or improvement in the lesions such that no further antimicrobial therapy was required. Thus, success combines those patients completely cured and those improved to some degree.

ii. "Failure" combines clinical response of failure at any time in the study with "unable to determine" patients (primarily those who did not attend the required visits).

Table 9. Clinical Response at Follow-up by Analysis Population

Analysis Population	SB-275833		Placebo		Difference in Success Rates (%)	95 % CI[2] (%)
	n/N[1]	Success Rate (%)	n/N[1]	Success Rate (%)		
ITTC	105/139	75.5	28/71	39.4	36.1	(22.7, 49.5)
PPC	98/119	82.4	25/58	43.1	39.2	(24.8, 53.7)
ITTB	91/114	79.8	19/57	33.3	46.5	(32.2, 60.8)
PPB	86/102	84.3	18/48	37.5	46.8	(31.4, 62.2)

1. n/N = number of successes/number of subjects that qualified for the respective analysis population in the respective treatment.
2. Confidence intervals were not adjusted for multiplicity.

Secondary Efficacy Results

i. Results at End of Therapy

The following table presents the success rates in the various defined populations at end of therapy. This is the sponsor's primary efficacy outcome.

Table 10. Clinical Response at End of Therapy by Analysis Population

Analysis Population	SB-275833		Placebo		Difference in Success Rates (%)	95% CI[2] (%)
	n/N[1]	Success Rate (%)	n/N[1]	Success Rate (%)		
ITTC	119/139	85.6	37/71	52.1	33.5	(20.5, 46.5)
PPC	111/124	89.5	33/62	53.2	36.3	(22.8, 49.8)
ITTB	101/114	88.6	28/57	49.1	39.5	(25.2, 53.7)
PPB	96/107	89.7	26/52	50.0	39.7	(25.0, 54.5)

1. n/N = number of successes/number of subjects that qualified for the respective analysis population in the respective treatment.
2. Confidence intervals were not adjusted for multiplicity.

ii. Signs and Symptoms

The following table presents the SIRS, or mean sign sign and symptom scores (All signs/symptoms totaled) at the baseline and test of cure (follow-up) visits. This presentation includes only those patients who were present for evaluation at the stated time point.

Table 11. Summary of SIRS Scores by Analysis Population

Analysis Population and Visit	Altabax		Placebo	
	n	Mean	n	Mean
ITT Visit 1	139	16.5	71	16.1
ITT Visit 3	120	1.2	38	1.3
PPC Visit 1	126	16.5	63	16.2
PPC Visit 3	107	1.0	31	1.5

Reviewer's Note: The above presentation was felt to be flawed because the high number of dropouts in the placebo group probably meant that the placebo results were more positive than would be expected if results from the failures who left the study early were included. Therefore, the sponsor was asked to provide an additional analysis in which the last observed value was carried forward. The additional analysis is presented below.

The following table presents the SIRS, or mean sign and symptom scores (all signs/symptoms totaled) at the baseline and the test of cure (follow-up) visits. In this presentation, the last observation is carried forward, including those for failures and other dropouts.

Table 12. Summary of SIRS Scores by Analysis Population

Analysis Population and Visit	Altabax		Placebo	
	n	Mean	n	Mean
ITT Visit 1	139	16.5	71	16.1
ITT Visit 3	139	2.6	71	8.1
PPC Visit 1	126	16.5	63	16.2
PPC Visit 3	119	2.0	58	8.9

Reviewer's Comment: The SIRS scores were lower on average at follow-up for the Altabax patients when the last observation was carried forward. The Applicant was asked to account for a slight discrepancy in the numbers of PPC patients in their data presentations. For example, there are 119 Altabax PPC patients listed in Table 9 above, while there are 126 listed in this table. The Applicant has replied that the higher number represents the PPC population at the baseline visit, while the lower number takes into consideration protocol violators during the study, and thus is the figure for the follow-up visit.

iii. Wound Size

The following table presents the mean and median wound size for the ITT and PPC analysis populations at baseline and the follow-up visit. The percent reduction refers to the total reduction in size in all wounds, rather than reduction in mean or median size. The sponsor states that the increase in lesion size in the placebo group is due to one patient who had a very large increase in lesion size over the course of the study. Again, the last observation is carried forward.

Table 13. Summary of Wound Size (cm^2) by Analysis Population

Analysis Population and Visit	Altabax				Placebo			
	n	Mean	Median	% Reduction	n	Mean	Median	% Reduction
ITT Visit 1	139	4.5	1.5	-	71	3.7	1.7	-
ITT Visit 3	139	1.1	0	75.6	71	4.7	0.2	-27.0
PPC Visit 1	126	4.7	1.5	-	63	4.0	1.5	-
PPC Visit 3	119	1.2	0	74.5	58	5.4	0.2	-35.0

Reviewer's Comment: It can be seen that when the wound sizes observed in patient failures are carried forward, Altabax was greatly superior in disease treatment. However, one placebo patient had a very large increase in lesion size, so these results should be interpreted cautiously.

iv. Subgroup Analyses

Demographic Factors

The sponsor has analyzed the clinical success at end of therapy (but not follow-up) in relationship to various baseline demographic factors, as follows.

Table 14. Clinical Response at End of Therapy by Subgroup Factors (ITTC Population)

Subgroup Factor	SB-275833		Placebo		Difference in Success Rates (%)
	n/N	Success Rate (%)	n/N	Success Rate (%)	
Clinical Diagnosis of Impetigo					
Bullous	20/26	76.9	6/11	54.5	22.4
Non-bullous	99/113	87.6	31/60	51.7	35.9
Primary Lesion Dressing Type at Baseline					
Occlusive	1/4	25.0	1/2	50.0	-25.0
Semi-Occlusive	3/4	75.0	2/2	100.0	-25.0
None	115/131	87.8	34/67	50.7	37.0
Age					
9 months - < 2 years	11/12	91.7	2/6	33.3	58.3
2 years - < 6 years	29/38	76.3	8/24	33.3	43.0
6 years - < 13 years	52/56	92.9	19/28	67.9	25.0
13 years - < 18 years	4/5	80.0	3/6	50.0	30.0
18 years - < 65 years	21/25	84.0	5/7	71.4	12.6
≥ 65 years	2/3	66.7	0	0	NA
Region					
Europe	34/42	81.0	9/18	50.0	31.0
International	85/97	87.6	28/53	52.8	34.8
Sex					
Male	57/66	86.4	21/37	56.8	29.6
Female	62/73	84.9	16/34	47.1	37.9
Race					
African American/ African Heritage	2/2	100.0	2/3	66.7	33.3
American Indian or Alaskan Native	21/23	91.3	5/13	38.5	52.8
Asian - Central/ South Asian Heritage	51/59	86.4	16/30	53.3	33.1
Mixed Race	1/1	100.0	2/2	100.0	0.0
White - Arabic/ North African Heritage	1/2	50.0	0	0.0	NA
White - White/ Caucasian/ European Heritage	43/52	82.7	12/23	52.2	30.5

Reviewer's Comment: It would have been preferable to have this information calculated at the follow-up visit. However, the primary efficacy analysis and other secondary analyses can be evaluated at follow-up. Therefore, this presentation is acceptable.

SIRS score ≥ 8 at follow-up

Because the review ([redacted] revealed that a number of patients had been declared clinical successes even though they finished the study with SIRS (signs and symptoms) scores ≥ 8, which is the SIRS score needed to enter the study, the FDA statistician was asked to provide an additional analysis. This analysis converted all patients who ended the study with SIRS scores ≥ 8 to failures, without regard to the outcome presented by the sponsor. The result of this analysis follows.

Table 15. Clinical Response at Follow-up by Analysis Population SIRS Score ≥ 8 as Failures

Analysis Population	SB-275833		Placebo		Difference in Success Rates (%)	95% CI (%)
	n/N	Success Rate (%)	n/N	Success Rate (%)		
PPC	98/119	82.4	25/58	43.1	39.2	(24.8, 53.7)
ITTC	105/139	75.5	28/71	39.4	36.1	(22.7, 49.5)

Reviewer's Comment: The results of this sensitivity analysis are consistent with and support the primary analysis.

Microbiological Efficacy

The following tables present microbiological and clinical success rates for the pathogens sought in the labeling (*S. aureus* and *S. pyogenes)*. Other pathogens are grouped. No MRSA isolates were identified.

Table 16. Clinical Success Rate of Follow-up by Baseline Pathogen (PPC Population)

Pathogen[1]	Altabax		Placebo		Difference in Success Rates (%)
	n/N[2]	Success Rate (%)	n/N[2]	Success Rate (%)	
S. aureus (all)	70/84	83.3	17/44	38.6	44.7
S. pyogenes	28/32	87.5	1/6	16.7	70.8
Other Strep. sp.	2/2	100	0	0	-
Other Gram (+)	1/1	100	0	0	-
Other Gram (-)	8/11	72.7	1/5	20	52.7
All pathogens	109/130	83.8	19/55	34.5	49.3
No pathogens	12/17	70.6	7/10	70	0.6

1. Individual pathogens not identified in 20 or more subjects were grouped
2. n/N = number of clinical success/number of pathogens present at baseline

Table 17. Microbiological Success Rate at Follow up by Baseline Pathogen (PPB Population)

Pathogen	Altabax		Placebo		Difference in Success Rates (%)
	n/N	Success Rate (%)	n/N	Success Rate (%)	
S. aureus (all)	71/84	84.5	19/44	43.2	41.3
S. pyogenes	29/32	90.6	2/6	33.3	57.3
Other Strep. sp.	2/2	100	0	0	-
Other Gram (+)	1/1	100	0	0	-
Other Gram (-)	8/11	77.7	1/5	20.0	52.7
All pathogens	111/130	85.4	22/55	40.6	45.4

1. Individual pathogens not identified in 20 or more subjects were grouped
2. n/N = number of clinical success/number of pathogens present at baseline

It should be noted that the outcomes in the preceding two tables are similar because in nearly all cases, the microbiological outcomes are presumed, based on the clinical progress of the patient.

Reviewer's Comment: There were no MRSA isolates identified in this patient population.

[redacted]

The sponsor was asked to provide information for the NDA reviewed here on the clinical success rate in the pivotal studies based on the presence of the PVL gene in both MRSA and MSSA isolates. The sponsor has replied that only MRSA isolates were tested for the presence of the PVL gene in the clinical studies in NDA 22-055.

[redacted]

In summary, this is a successful study. Altabax was dramatically superior to its placebo when used twice daily for 5 days in the treatment of impetigo caused by *S. aureus* and *S. pyogenes*. The study was small in size (210 patients) but Altabax was 35-40% superior to placebo in all analysis populations and the study results were statistically robust. Forty-four percent of the placebo patients did not finish the study, mostly due to lack of efficacy and disease progression. Nonetheless, this study suggests that placebo-controlled studies can be performed in relatively minor skin infection disorders. Given the large treatment effect over placebo, however, ethical questions must be addressed for each contemplated study of this type, and in most cases, studies with an active control will probably be preferable.

6.1.4.2 Study TOC 100224

1. Disposition of subjects: A total of 519 subjects were randomized into the study at a ratio of 2 Altabax to 1 sodium fusidate. The following table presents the disposition of these subjects.

Table 18. Subject Disposition

Subject Disposition	Treatment		Total
	SB-275833	Sodium Fusidate	
Randomized	346	173	519
Randomized but not treated	1	1	2
Completed Study	319	157	476

The following table presents the reasons for early withdrawal from the study.

Table 19. Number (%) of Subjects Withdrawn from the Study by Reason for Withdrawal (ITTC Population)

Reason for Withdrawal	Treatment Group		
	SB-275833 N= 139	Sodium Fusidate N= 71	Total N= 210
	n (%)	n (%)	n (%)
Completed Study	319 (92)	157 (91)	476 (92)
Prematurely Withdrawn	26 (8)	15 (9)	41 (8)
Disease progression	8 (2)	6 (3)	14 (3)
Lost to Follow-Up	8 (2)	1 (<1)	9 (2)
Other	3 (<1)	3 (2)	6 (1)
Subject decided to withdraw from study	3 (<1)	1 (<1)	4 (<1)
AE	1 (<1)	3 (2)	4 (<1)
Lack of Efficacy	1 (<1)	1 (<1)	2 (<1)
Protocol violation	1 (<1)	0	1 (<1)
Sponsor terminated study	1 (<1)	0	1 (<1)

The discontinuances due to adverse events will be discussed in the safety section below.

The following table summarizes the number of patients analyzed in the various cohorts. Please note that Table 19 above only concerns withdrawals, so the total that completed the study is not the same as the per protocol total.

Table 20. Summary of Analysis Populations

Analysis Population	SB- 275833 (N = 345)	Sodium Fusidate (N = 172)	Total (N = 517)
Intent-to-Treat Clinical Population	345 (100.0%)	172 (100.0%)	517 (100.0%)
Per Protocol Clinical	308 (89.3%)	143 (83.1%)	451 (87.2%)
Reason for PP Exclusion			
Inclusion or exclusion criteria not met	1 (0.3%)	2 (1.2%)	3 (0.6%)
Less than 80% study medication compliance	1 (0.3%)	7 (4.1%)	8 (1.5%)
Did not return for scheduled FU visit	1 (0.3%)	0 (0.0%)	1 (0.2%)
Was exposed to other topical treatment	10 (2.9%)	7 (4.1%)	17 (3.3%)
Relative day is not in a specified visit window	7 (2.0%)	10 (5.8%)	17 (3.3%)
Clinical response was UTD[1]	19 (5.5%)	2 (1.2%)	21 (4.1%)
Subject received the wrong medication	1 (0.3%)	0 (0.0%)	1 (0.2%)
Intent-to Treat Bacteriological Population	263 (76.2%)	131 (76.2%)	394 (76.2%)
Reason for ITTB Exclusion			
Isolate not sent to central laboratory	3 (0.9%)	0 (0.0%)	3 (0.6%)
No Baseline Pathogen Isolated	79 (22.9%)	41 (23.8%)	120 (23.2%)
Per Protocol Bacteriological [2]	235 (68.1%)	107 (62.2%)	342 (66.2%)
Reason for PPB Exclusion			
Inclusion or exclusion criteria not met	1 (0.3%)	2 (1.2%)	3 (0.6%)
Less than 80% study medication compliance	1 (0.3%)	5 (2.9%)	6 (1.2%)
Did not return for scheduled FU visit	1 (0.3%)	0 (0.0%)	1 (0.2%)
Was exposed to other topical treatment	7 (2.0%)	4 (2.3%)	11 (2.1%)
Relative day is not in a specified visit window	5 (1.4%)	10 (5.8%)	15 (2.9%)
Clinical response was UTD[1]	14 (4.1%)	2 (1.2%)	16 (3.1%)
Subject received the wrong medication	1 (0.3%)	0 (0.0%)	1 (0.2%)

(1) UTD = Unable to Determine (2) Subjects in the PPB population are those from the ITTB population without protocol violations.

2. Investigators: This was a multi-center study conducted at 37 independent sites in 9 countries under a common protocol. There were 12 sites in Germany, 6 in South Africa, 4 in Canada, 5 in the Netherlands, 4 in France, 3 in India, and one each in Peru, Poland and Costa Rica. The following presentation lists the principal clinical investigators and the sponsor's intent-to-treat patient population enrollment by investigator. The presentation also lists the number of patients who were clinically and microbiologically evaluable. The table does not list investigators who had no evaluable patients.

The percentages in the following table represent the following:

-The percentage figure following the ITT number is the proportion of the total ITT population enrolled by that investigator.

-The percentage following the clinically and microbiologically evaluable numbers are the proportions of the patients evaluable for that cohort by center, based on the ITT population for that investigator.

Table 21. Subject Accountability by Investigator

Study Center/ Investigator/ Location	ITT Analysis (n) (% of total ITT population)	Clinically Evaluable (n) (% of Center population)	Micro Evaluable (n) (% of Center population)
[redacted] Ontario, Canada	4 (0.8)	2 (50)	0
[redacted] Ontario, Canada	3 (0.6)	3 (100)	2 (66)
[redacted] Labrador, Canada	2 (0.4)	1 (50)	1 (50)
[redacted] Ontario, Canada	7 (1.4)	5 (71)	1 (14)
[redacted] San Jose, Costa Rica	40 (7.7)	40 (100)	23 (58)
[redacted] Mumbai, India	40 (7.7)	38 (95)	35 (88)
[redacted] Karnataka, India	31 (6.0)	30 (97)	20 (65)
[redacted] Karnataka, India	58 (11.2)	53 (91)	40 (69)
[redacted] Cape Town, South Africa	36 (7.0)	33 (92)	26 (72)
[redacted] Cape Town, South Africa	44 (8.5)	36 (82)	36 (82)
[redacted] Pretoria, South Africa	18 (3.5)	17 (94)	11 (61)

[redacted] Pretoria, South Africa	9 (1.7)	6 (66)	5 (56)
[redacted] Lima, Peru	35 (6.8)	32 (91)	29 (83)
[redacted] Sittard, Netherlands	6 (1.1)	4 (66)	3 (50)
[redacted] Zwijndrecht, Netherlands	14 (2.4)	8 (57)	7 (50)
[redacted] Soerendonk, Netherlands	2 (0.4)	1 (50)	1 (50)
[redacted] Musselkanaal, Netherlands	6 (1.1)	5 (83)	4 (66)
[redacted] Martiques, France	4 (0.8)	1 (25)	0
[redacted] Paris, France	4 (0.8)	4 (100)	0
[redacted] Conde, France	13 (2.5)	11 (85)	8 (62)
[redacted] Bersee, France	1 (0.2)	1 (100)	1 (100)
[redacted] Grudziadz, Poland	12 (2.3)	9 (75)	7 (58)
[redacted] Ermelo, Netherlands	1 (0.2)	1 (100)	1 (100)
[redacted] Johannesburg, South Africa	45 (8.7)	42 (93)	31 (69)
[redacted] Johannesburg, South Africa	14 (2.7)	14 (100)	14 (100)
[redacted] Kiel, Germany	4 (0.8)	3 (75)	1 (25)
[redacted] Krefeld, Germany	1 (0.2)	1 (100)	1 (100)

[redacted] Berlin, Germany	5 (1.0)	5 (100)	5 (100)
[redacted] Mahlow, Germany	8 (1.5)	7 (88)	3 (38)
[redacted] Unna, Germany	2 (0.4)	2 (100)	1 (50)
[redacted] Dülmen, Germany	4 (0.8)	4 (100)	4 (100)
[redacted] Materborn, Germany	2 (0.4)	2 (100)	2 (100)
[redacted] Augsburg, Germany	20 (3.9)	15 (75)	8 (40)
[redacted] Schmiedeberg, Germany	8 (1.5)	7 (88)	5 (63)
[redacted] Deudsburg, Germany	3 (0.6)	2 (66)	2 (66)
[redacted] Düsseldorf, Germany	3 (0.6)	3 (100)	3 100)
[redacted] Preetz, Germany	3 (0.6)	3 (100)	1 (33)

Reviewer's Comment: **About half of the patients in this study came from India or South Africa.**

3. Demographics: The following table provides the demographic characteristics of the ITT population by test cohort.

Table 22. Demographic Characteristics (ITTC Population)

Demographic Characteristic	Treatment Group		Total
	SB-275833	Sodium Fusidate	
	N = 345	N = 172	N=517
Age, (yr)			
Mean (SD)	17.8 (19.4)	14.4 (15.7)	16.7 (18.3)
Median	9.0	7.0	8.0
Range	0-84	0-66	0-84
Gender, n (%)			
Female	167 (48)	72 (42)	239 (46)
Male	178 (52)	100 (58)	278 (54)
Race, n (%)			
African American/ African heritage	92 (27)	48 (28)	140 (27)
American Indian or Alaskan native	25 (7)	11 (6)	36 (7)
Asian - Central/ South Asian heritage	85 (25)	44 (26)	129 (25)
Asian - South East Asian heritage	1 (<1)	3 (2)	4 (<1)
White - Arabic/ North African heritage	2 (<1)	1 (<1)	3 (<1)
White - White/ Caucasian/ European heritage	140 (41)	65 (38)	205 (40)
Ethnicity, n (%)			
Hispanic/ Latino	56 (16)	24 (14)	80 (15)
Not Hispanic/ Latino	289 (84)	148 (86)	437 (85)
Age Strata			
9 months - <2 years	29	12	41
2 years - < 6 years	90	53	143
6 years - <13 years	87	47	134
13 years - < 18 years	27	14	41
18 years - <65 years	97	45	142
≥ 65 years	15	1	16

The following table presents the impetigo diagnosis (bullous vs. non-bullous) in the populations analyzed.

Table 23. Clinical Diagnosis of Impetigo at Baseline in Each Analysis Population

Demographic Characteristic	Treatment Group	
	SB-275833	Sodium Fusidate
Bullous, n (%)		
ITTC	75 (21.7)	35 (20.3)
PPC	67 (21.8)	28 (19.6)
ITTB	61 (23.2)	28 (21.4)
PPB	53 (22.6)	21 (19.6)
Non-bullous, n (%)		
ITTC	270 (78.3)	137 (79.7)
PPC	241 (78.2)	115 (80.4)
ITTB	202 (76.8)	103 (78.6)
PPB	182 (77.4)	86 (80.4)

4. Effectiveness Parameters

Reviewer's Comment: The applicant's database was not audited for this study because the reviewer did not consider it to be a pivotal study. The reasons for this are as follows:

1. **Since sodium fusidate is not approved in this country, the reviewer must regard it as a placebo in the context of data analysis. Therefore, in order for the study to be acceptable as a pivotal study in the U.S., it is necessary that Altabax be superior to sodium fusidate. While for the Applicant's primary efficacy parameter, clinical response at end of therapy, Altabax was statistically superior to sodium fusidate, for the reviewer's preferred primary efficacy parameter, clinical response at follow-up, the Applicant's analysis indicates that Altabax is not superior to sodium fusidate. Therefore, the results cannot be accepted as proof of efficacy of Altabax.**

2. **Even if the above were not true, the blinding procedures for the study are questionable. The products were not identical in appearance and the dosage regimens were dissimilar (Altabax BID for 5 days, sodium fusidate TID for 7 days). This necessitated a single-blind (evaluator-blinded) study.**

Primary Efficacy Results- Clinical Response at Follow-up

The following table presents the success rates in the various defined populations at follow-up. This is the reviewer's primary efficacy outcome for this study. Please also see the comments under this heading for Study 103469 concerning definitions of success and failure.

Table 24. Clinical Response at Follow-up by Analysis Population

Analysis Population	SB-275833		Sodium Fusidate		Difference in Success Rates (%)	95% CI (%)[1]
	n/N	Success Rate (%)	n/N	Success Rate (%)		
ITTC	310/345	89.9	150/172	87.2	2.6	(-3.3, 8.6)
PPC	297/308	96.4	134/143	93.7	2.7	(-1.8, 7.2)
ITTB	237/263	90.1	111/131	84.7	5.4	(-1.8, 12.5)
PPB	227/235	96.6	99/107	92.5	4.1	(-1.4, 9.6)

1. Confidence intervals were not adjusted for multiplicity

Secondary Efficacy Results

i. Results at End of Therapy

The following table presents the success rates in the various defined populations at end of therapy. This is the sponsor's primary efficacy outcome.

Table 25. Clinical Response at End of Therapy by Analysis Population

Analysis Population	SB-275833		Sodium Fusidate		Difference in Success Rates (%)	95% CI (%)
	n/N	Success Rate (%)	n/N	Success Rate (%)		
ITTC	327/345	94.8	155/172	90.1	4.7	(-0.4,9.7)[1]
PPC	314/317	99.1	141/150	94.0	5.1	(1.1, 9.0)
ITTB	250/263	95.1	116/131	88.5	6.5	(1.4, 11.0)
PPB	240/242	99.2	106/114	93.0	6.2	(0.5, 12.6)

1. Due to high efficacy rate, the normality assumption may not have been valid.

ii. Signs and Symptoms

The following table presents the SIRS, or mean sign and symptom scores (all signs/symptoms totaled) at base line and test of cure (follow-up) visits.

Table 26. Summary of SIRS Scores by Analysis Population

Analysis Population and Visit	Altabax		Sodium Fusidate	
	n	Mean	n	Mean
ITT Visit 1	345	16.1	172	16.3
ITT Visit 4	329	0.4	161	0.4
PPC Visit 1	319	16.0	152	16.1
PPC Visit 4	301	0.3	139	0.3

iii. Wound Size

The following table presents the mean and median wound size for the ITT and PPC analysis populations at baseline and the follow-up visits. The percent reduction refers to the total reduction in size in all wounds, rather than reduction in mean or median size.

Table 27. Summary of Wound Size (cm^2) by Analysis Population

Analysis Population and Visit	Altabax				Sodium Fusidate			
	n	Mean	Median	% Reduction	n	Mean	Median	% Reduction
ITT Visit 1	345	6.9	2.0	-	172	6.4	2.0	-
ITT Visit 4	329	0.4	0	91.7	160	0.5	0	77.1
PPC Visit 1	319	6.4	2.0	-	152	6.4	2.6	-
PPC Visit 4	308	0.4	0	95.6	138	0.6	0	77.3

Reviewer's Comment: Altabax reduced the total area of diseased skin more effectively than did sodium fusidate.

iv. Subgroup Analyses

Demographic Factors

The sponsor has analyzed the clinical success at end of therapy (but not follow-up) in relationship to various demographic factors, as follows:

Table 28. Clinical Response at End of Therapy by Subgroup Factors (PPC Population)

Subgroup Factor	SB-275833 n/N	SB-275833 Success Rate (%)	Sodium Fusidate n/N	Sodium Fusidate Success Rate (%)	Difference in Success Rates (%)
Clinical Diagnosis of Impetigo					
Bullous	69/70	98.6	27/29	93.1	5.5
Non-bullous	245/247	99.2	114/121	94.2	5.0
Primary Lesion Dressing Type at Baseline					
Occlusive	21/21	100	10/11	90.9	9.1
Semi-Occlusive	30/30	100	10/13	76.9	23.1
None	263/266	98.9	121/126	96.0	2.8
Age					
9 months - < 2 years	27/27	100	9/10	90.0	10.0
2 years - < 6 years	81/82	98.8	49/52	94.2	4.5
6 years - < 13 years	79/80	98.8	35/37	94.6	4.2
13 years - < 18 years	25/25	100	9/11	81.8	18.2
18 years - < 65 years	87/88	98.9	38/39	97.4	1.4
≥ 65 years	15/15	100	1/1	100	0
Region					
Canada & Europe	88/88	100	30/34	88.2	11.8
International	226/229	98.7	111/116	95.7	3.0
Sex					
Male	165/166	99.4	81/84	96.4	3.0
Female	149/151	98.7	60/66	90.9	7.8
Race					
African American/ African Heritage	85/87	97.7	38/41	92.7	5.0
American Indian or Alaskan Native	22/22	100	10/11	90.9	9.1
Asian - Central/ South Asian Heritage	79/79	100	43/43	100	0
Asian - South East Asian Heritage	1/1	100	1/1	100	0
White - Arabic/ North African Heritage	2/2	100	1/1	100	0
White - White/ Caucasian/ European Heritage	125/126	99.2	48/53	90.6	8.6

Reviewer's Comment: It would have been preferable to have this information calculated at the follow-up visit.

SIRS score ≥ 8 as failure

Because the review of [redacted] revealed that a number of patients had been declared clinical successes even though they finished the study with SIRS (sign and symptom scores) ≥ 8, which is the SIRS score needed to enter the study, the FDA statistician was asked to provide an additional analysis. This analysis converted all patients who ended the study with SIRS scores ≥ 8 to failures without regard to the outcome presented by the sponsor. The result of this analysis is as follows:

Table 29. Clinical Response at Follow-Up by Analysis Population – SIRS Score ≥ 8 as Failures

Analysis Population	SB-275833		Sodium Fusidate		Difference in Success Rates (%)	95% CI (%)
	n/N	Success Rate (%)	n/N	Success Rate (%)		
PPC	296/308	96.1	134/143	93.7	2.4	(-2.1, 6.9)
ITTC	309/345	89.6	150/172	87.2	2.4	(-3.6, 8.3)

Microbiological Efficacy

The following tables present microbiological and clinical success rates for the pathogens sought in the labeling (*S. aureus* and *S. pyogenes*). Other pathogens are grouped.

Table 30. Clinical Success Rate of Follow-up by Baseline Pathogen (PPC Population)

Pathogen[1]	Altabax		Sodium Fusidate		Difference in Success Rates (%)
	n/N[2]	Success Rate (%)	n/N[2]	Success Rate (%)	
S. aureus (all)	199/206	96.6	83/90	92.2	4.4
MRSA[3]	8/8	100	2/2	100	0
MSSA[3]	191/198	96.5	81/88	92.0	4.4
S. pyogenes	87/91	95.6	31/36	86.1	9.5
Other Strep. sp.	4/4	100	3/3	100	0
Other Gram (+)	3/3	100	1/1	100	0
Other Gram (-)	12/14	85.7	14/16	87.5	-1.8
All pathogens	305/318	95.9	132/146	90.4	5.5
No pathogens	70/73	95.9	35/36	97.2	-1.3

1. Individual pathogens not identified in 20 or more subjects were grouped
2. n/N = number of clinical success/number of pathogens present at baseline
3. MRSA/MSSA are methicillin resistant/ susceptible *S. aureus* as defined by susceptibility to oxacillin.

Table 31. Microbiological Success Rate at Follow-up by Baseline Pathogen (PPB Population)

Pathogen[1]	Altabax		Sodium Fusidate		Difference in Success Rates (%)
	n/N[2]	Success Rate (%)	n/N[2]	Success Rate (%)	
S. aureus (all)	199/206	96.6	84/90	93.3	3.3
MRSA[3]	8/8	100	2/2	100	0
MSSA[3]	191/198	96.5	82/88	93.2	3.3
S. pyogenes	87/91	95.6	32/36	88.9	6.7
Other Strep. sp.	4/4	100	3/3	100	0
Other Gram (+)	3/3	100	1/1	100	0
Other Gram (-)	12/14	85.7	14/16	87.5	-1.8
All pathogens	305/318	95.9	132/146	91.8	4.1

1. Individual pathogens not identified in 20 or more subjects were grouped
2. n/N = number of clinical success/number of pathogens present at baseline
3. MRSA/MSSA are methicillin resistant/ susceptible *S. aureus* as defined by susceptibility to oxacillin.

Reviewer's Comment: All ten MRSA isolates in this study were successfully treated. Four of them were PVL positive. Please see the comments under the placebo controlled study above concerning possible influence of the PVL gene on the effectiveness of Altabax against *S. aureus*.

In summary, this may not be considered a successful pivotal study, as follows:

1. The study was designed to demonstrate the non-inferiority of Altabax to sodium fusidate ointment in the treatment of impetigo. However, sodium fusidate is not approved in the U.S. and so its ability to treat impetigo has not been established for the purpose of comparing it to another drug. Therefore, it is necessary to regard sodium fusidate as a placebo in performing the regulatory review. Under these circumstances, Altabax would have to be superior to sodium fusidate for the study to have a successful outcome. By the Applicant's own analysis , the test products are not statistically different in clinical outcome at the follow-up visit, which is the reviewer's primary efficacy outcome. The study is acceptable as a well-performed supportive study.

2. The blinding techniques used in the study are questionable. Because the test products are dissimilar in physical appearance, this is a single-blind (evaluator-blind) study. Further, the two products had different dosage regimens (Altabax BID for 5 days, sodium fusidate TID for 7 days). This necessitated two "end of therapy" visits 2 days apart, while all patients had a follow-up visit at the same time (14 days). It is reasonable to assume under these conditions that breaking of the blind occurred more frequently than would be expected in a double-blind study, which may have introduced bias into the outcome.

3. The difficulties with this study design are illustrated by the differences seen in clinical success rates in the placebo controlled and sodium fusidate controlled studies. In roughly similar patient populations successful results for Altabax were about 14%

higher in the sodium fusidate controlled study. There is no obvious explanation for this difference other than the investigator's awareness of the structure of the study, with the resultant expectation that all patients will improve.

6.1.5 Clinical Microbiology

This review is not yet available. Please see the review of [redacted] for previous information concerning the microbiological characteristics of retapamulin.

6.1.6 Efficacy Conclusions

Adequate evidence is available to establish the effectiveness of Altabax in impetigo. The single acceptable pivotal study establishes that Altabax is dramatically superior to placebo when used twice daily for 5 days. The study was well designed. Though the number of patients studied was relatively small, Altabax proved to be at least 30% more successful than placebo in achieving clinical success at the reviewer's primary efficacy evaluation, the follow-up visit.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The applicant has demonstrated that Altabax is relatively safe for the proposed indication of impetigo. In the two pivotal studies submitted, 484 patients were exposed to Altabax Ointment, 71 to placebo and 172 to sodium fusidate ointment. Though the studies were differently designed, the use of Altabax was consistent in both studies, which permits combination of the Altabax safety results over both patient cohorts. Adverse events were reported using MedDra terminology.

The dose and projected skin area to be covered for impetigo patients are similar to those recommended for use in [redacted]. Reference is made to that NDA for the results of studies concerning human irritation, sensitization, and systemic effects. The present submission does contain results from clinical laboratory evaluations, but not QT effects.

7.1.1 Deaths

There were no deaths in the impetigo studies.

7.1.2 Other Serious Adverse Events (SAE's)

There were 3 SAE's reported in Altabax patients in the combined impetigo studies: one each abnormal coordination, eczema herpeticum, and worsening of impetigo. The investigators did not feel that any of these events were related to the drug. Review of the summaries submitted for the SAE's suggest the report of abnormal coordination was indeed not related to Altabax. The reports of worsening impetigo and eczema herpeticum occurred in the same patient, a 5-year-old

male. The report is somewhat lacking in detail, but the worsening impetigo could logically be associated with lack of drug effect. Because Altabax lacks antiviral activity, it is difficult to assign lack of effectiveness to the eczema herpeticum outbreak.

There were no SAE's in the placebo or sodium fusidate patients.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The most common reasons for dropouts in the clinical studies were lack of efficacy/disease progression (49/727=6.7% of ITT patients).

7.1.3.2 Adverse events associated with dropouts

The following table presents the number of patients in the impetigo studies who withdrew due to adverse events.

Table 32. Summary of Adverse Events Leading to Study Withdrawal
(ITTC Population: Studies TOC 103469 and TOC 100224 Combined)

Preferred Term	Number (%) of Subjects		
	SB-275833 N = 484	Sodium Fusidate N = 172	Placebo N=71
Any Leading to Withdrawal	2 (<1)	3 (2)	1 (1)
Application site pruritus	1 (<1)	0	0
Edema mucosal	1 (<1)	0	0
Hypersensitivity	0	1 (<1)	0
Infection	0	1 (<1)	0
White blood cell count increased	0	1 (<1)	0
Pharyngitis bacterial	0	0	1 (1)

Review of the summaries submitted for the AE's which led to study withdrawal suggest that the application site pruritus was related to use for Altabax. Additionally, the hypersensitivity in the sodium fusidate patient was probably related to the drug.

7.1.3.3 Other significant adverse events

None.

7.1.4 Other Search Strategies

The case report forms were reviewed for additional safety information, but none was found.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse event data in the development program

The patients were assessed for adverse effects at each study visit.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The adverse event categorization and preferred terms are commonly used and are acceptable.

7.1.5.3 Incidence of common adverse events

The number of subjects with adverse events in the impetigo studies is presented in the following table.

Table 33. Number of Subjects (%) with Adverse Events
(ITTC Population: Studies TOC 103469 and TOC 100224 Combined)

	Number (%) of Subjects		
	SB-275833 N = 484	**Sodium Fusidate N = 172**	**Placebo N=71**
Any Adverse Event	90 (19)	25 (15)	18 (25)
Drug-Related Adverse Event	26 (5)	1 (<1)	2 (3)
Serious Adverse Event	2 (<1)	0	0
Adverse Events Leading to Withdrawal	2 (<1)	3 (2)	1 (1)

7.1.5.4 Common adverse event tables

The following table presents a summary of the most common adverse events in the impetigo studies.

Table 34. Most Common AEs (Greater than 1%) in Any Treatment Group (ITTC Population: Studies TOC 103469 and TOC 100224 Combined)

Preferred Term	Number (%) of Subjects		
	SB-275833 N = 484	**Sodium Fusidate N = 172**	**Placebo N=71**
Any Adverse Event	91 (19)	25 (15)	18 (25)
Application site pruritus	13 (3)	0	1 (1)
Headache	9 (2)	0	0
Application site irritation	8 (2)	0	1 (1)
Excoriation	2 (<1)	4 (2)	0
Urinary tract infection	0	4 (2)	0
Impetigo	2 (<1)	0	2 (3)
Xerosis	0	0	2 (3)

The following table combines the most common AE's seen in the impetigo studies for Altabax (see Table 34) and compares them to the most common AE's seen in the 3 pivotal studies submitted in support [redacted]

Table 35. Most Common AE's for Altabax Ointment in the Combined Impetigo Studies vs. the Combined Pivotal Studies for [redacted]

Preferred Term	Number (%) of Subjects	
	Impetigo Studies N = 484	[redacted] Studies N = 1631
Any adverse event	91 (19)	368 (23)
Headache	9 (2)	27 (2)
Application site irritation	8 (2)	22 (1)
Application site pruritus	13 (3)	8 (<1)
Application site paresthesia	4 (1)	0
Pruritus	4 (1)	9 (<1)
Diarrhea	4 (1)	27 (2)
Nasopharyngitis	3 (<1)	24 (1)
Nausea	0	19 (1)

7.1.5.5 Identifying common and drug-related adverse events

The following table presents a summary of the drug-related adverse events (as evaluated by the investigator) for the impetigo studies.

Table 36. Summary of Drug-related Adverse Events
(ITTC Population: Studies TOC 103469 and TOC 100224 Combined)

Preferred Term	Number (%) of Subjects		
	SB-275833 N = 484	Sodium Fusidate N = 172	Placebo N=71
Any drug-related AE, n (%)	26 (5)	1 (<1)	2 (3)
Application site pruritus	11 (2)	0	1 (1)
Application site irritation	8 (2)	0	0
Application site paresthesia	4 (<1)	0	1 (1)
Pruritus	3 <1)	0	0
Application site pain	2 (<1)	0	0
Diarrhea	1 (<1)	0	0
Dry skin	1 (<1)	0	0
Eosinophilla	1 (<1)	0	0
Eye irritation	1 (<1)	0	0
Headache	1 (<1)	0	0
Paresthesia	1 (<1)	0	0
Skin irritation	1 (<1)	0	0
Hypersensitivity	0	1 (<1)	0

The following table combines the most common drug-related AE's seen in the impetigo studies (see Table 36 above) and compares them to the most common drug-related AE's seen in [redacted]

Table 37. Most Common Drug-Related AE's for Altabax Ointment in the Combined Impetigo Studies vs. the Combined Pivotal Studies for [redacted]

Preferred Term	Number (%) of Subjects	
	Impetigo Studies N = 484	[redacted] Studies N = 1631
Application site irritation	8 (2)	21 (1)
Application site pruritus	11 (2)	7 (<1)
Application site paresthesia	4 (<1)	0
Pruritus	3 (<1)	4 (<1)
Diarrhea	1 (<1)	18 (1)
Application site pain	2 (<1)	5 (<1)
Headache	1 (<1)	6 (<1)

Reviewer's Comment: There are no new or unusual toxicities seen in the impetigo studies. It is noted that application site pruritus and irritation are more common in the impetigo studies than in the studies submitted in support of [redacted]. The reason for this is not clear.

7.1.5.6 Additional analyses and explorations

None.

7.1.6 Less Common Adverse Events

Adverse events in the clinical studies were not frequent and followed no pattern. The following listing includes the total numbers of patients in the clinical studies by system organ class who had adverse events in those classes.

Table 38. Adverse Events by System Organ Class and Decreasing Incidence
(ITTC Population: Studies TOC 103469 and 100224 Combined)

MedDra AE Coding Dictionary System Organ Class	Number (%) of Subjects		
	SB-275833 N = 484	Sodium Fusidate N = 172	Placebo N=71
Any AE, n (%)	90 (19)	25 (15)	18 (25)
General disorders and administration site conditions	27 (6)	1 (<1)	6 (8)
Infections and infestations	24 (5)	9 (5)	5 (7)
Skin and subcutaneous tissue disorders	13 (3)	4 (2)	3 (4)
Nervous system disorders	12 (2)	0	1 (1)
Injury, poisoning, and procedural complications	8 (2)	8 (5)	0
Gastrointestinal disorders	7 (1)	2 (1)	2 (3)
Blood and lymphatic system disorders	5 (1)	0	0
Respiratory, thoracic, and mediastinal disorders	4 (<1)	1 (<1)	0
Eye disorders	4 (<1)	0	0
Musculoskeletal and connective tissue disorders	2 (<1)	0	1 (1)
Immune system disorders	1 (<1)	1 (<1)	0
Metabolism and nutrition disorders	1 (<1)	0	1 (1)
Renal and urinary disorders	1 (<1)	0	0
Psychiatric disorders	1 (<1)	0	0
Ear and labyrinth disorders	1 (<1)	0	0
Reproductive system and breast disorders	1 (<1)	1 (<1)	0

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

In the clinical studies described in this review, routine hematology testing and clinical chemistry tests were performed at baseline and on day 7. This was 2 days after therapy ended for Altabax and placebo patients and the last day of therapy for sodium fusidate patients.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The laboratory values for both clinical studies were examined in a combined analysis.

7.1.7.3 Standard analyses and explorations of laboratory data

The following table presents the results of these determinations in terms of comparison with normal ranges for the clinical studies. There were no large mean changes from baseline during the studies for the total population or individual age groups. The "Values of Interest" were chosen by the Independent Data Monitoring Committee [redacted].

Table 39. End of Therapy Shifts from Baseline in Clinical Laboratory Values of Interest (ITTC: Population: Studies TOC 103469 and TOC 100224 Combined)

Parameter	Shift from Normal to:	SB-275833[1]	Sodium Fusidate[2]	Placebo[2]
Subject <18 years of age				
		N = 344 n/N[3] (%)	**N= 126 n/N[3] (%)**	**N = 64 n/N[3] (%)**
Blood Glucose	High	17/273 (6)	2/99 (2)	4/40 (10)
	Low	4/273 (1)	4/99 (4)	1/40 (3)
Eosinophil Count	High	24/259 (9)	3/98 (3)	1/36 (3)
	Low	6/259 (2)	0	0
GGT	High	0	1/99 (1)	0
	Low	0	0	0
Subjects 18 to <65 years of age				
		N = 122 n/N[3] (%)	**N = 45 n/N[3] (%)**	**N = 7 n/N[3] (%)**
Blood Glucose	High	7/110 (6)	3/38 (8)	1/7 (14)
	Low	6/110 (5)	1/38 (3)	0
Eosinophil Count	High	0	0	0
	Low	3/107 (3)	3/36 (8)	0
GGT	High	1/110 (<1)	0	0
	Low	0	0	0
Subjects ≥ 65 years of age				
		N = 18 n/N[3] (%)	**N = 1 n/N[3] (%)**	**N = 0 n/N[3] (%)**
Blood Glucose	High	2/16 (13)	1/1 (100)	-
	Low	1/16 (6)	0	-
Eosinophil Count	High	0	0	-
	Low	2/15 (13)	0	-
GGT	High	0	0	-
	Low	0	0	-

1. At Day 7 to 9 (Visit 3)
2. At Day 7 to 9 (Visit 2)
3. N = number of subjects with laboratory values at baseline

The following table presents clinically significant laboratory values for all pivotal studies combined. In the table, N= the number of subjects with the lab test result in question in the defined normal range, while Tot = the total number of subjects with that lab test result at baseline and post baseline visits.

Table 40. Clinically Significant Laboratory Values (Studies TOC 103469 and 100224 Combined)

Laboratory Parameter	Clinically Significant Lab Compared to Baseline)	SB-275833			Sodium Fusidate			Placebo		
		N	Tot	%	N	Tot	%	N	Tot	%
Bilirubin, Total (UMOL/L)	>1x to 2x ULN	3	359	0.8	3	118	2.5	0	47	0
	>=2x to 3x ULN	1	359	0.3	0	118	0	0	47	0
	>=3x ULN	0	359	0	0	118	0	0	47	0
CPK (IU/L)	No values	No values			No values			No values		
Creatinine (UMOL/L)	>1x to 2x ULN	0	358	0	2	118	1.7	0	47	0
	>=2x ULN	0	358	0	0	118	0	0	47	0
SGOT/AST (IU/L)	>1x to 3x ULN	3	353	0	7	116	6.0	0	45	0
	>=3x to 6x ULN	1	353	0.3	0	116	0	0	45	0
	>=6x ULN	1	353	0.3	1	116	0.9	0	45	0
SGPT/ALT (IU/L)	>1x to 3x ULN	3	358	0.8	4	119	3.4	0	47	0
	>=3x to 6x ULN	2	358	0.6	0	119	0	0	47	0
	>=6x ULN	1	358	0.3	1	119	0.8	0	47	0
Absolute Eosinophil Count (GI/L)	>1x to 2x ULN	45	335	13.4	9	115	7.8	8	39	20.5
	>=2x ULN	12	335	3.6	5	115	4.3	0	39	0
Absolute Neutrophil Count (GI/L)	Count <=1000	0	335	0	0	115	0	0	39	0
	Count <=500	0	335	0	0	115	0	0	39	0
Hemoglobin (G/L)	Decrease of >=2	3	327	0.9	2	123	1.6	2	37	5.4

There was one subject in the Altabax treatment group in Study 100224 who had a normal SGOT value at baseline (39 IU/L) and an increased value (352 IU/L) at visit 2. There was also one Altabax patient in this study with a normal eosinophil count at baseline and an abnormal one at the subsequent visit. All other subjects with clinically significant abnormal values after baseline also had abnormal values at baseline.

Reviewer's Comment: None of the patients with abnormal liver function tests meet the criteria predicting drug-induced liver injury (DILI) as outlined in the draft Concept Paper concerning evaluation of DILI prepared by the Hepatotoxicity Working Group from CDER/CBER. These results do not suggest that use of Altabax has the potential to affect laboratory values in a clinically significant manner.

7.1.7.4 Additional analyses and explorations

None.

7.1.7.5 Special assessments

None.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs were taken only at baseline for purpose of study eligibility.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Not applicable.

7.1.8.3 Standard analyses and explorations of vital signs data

Not applicable.

7.1.8.4 Additional analyses and explorations

Not applicable.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

ECG testing was not done as part of the impetigo testing program. [redacted]

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Not applicable.

7.1.9.3 Standard analyses and explorations of ECG data

Not applicable.

7.1.9.4 Additional analyses and explorations

Not applicable.

7.1.10 Immunogenicity

The ability of retapamulin to simulate an immune response has not been defined. Immune responses were not noted in the absorption studies performed in support of [redacted].

7.1.11 Human Carcinogenicity

No studies of this type were performed, nor are they considered necessary as the product is intended for short-term use.

7.1.12 Special Safety Studies

Not applicable. Please see [redacted] for results of human irritation, sensitization and pharmacokinetic studies with retapamulin.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

These phenomena are not applicable to this drug.

7.1.14 Human Reproduction and Pregnancy Data

There is no formal information concerning the use of Altabax in pregnant women. The pregnancy category for the drug is "B", based on animal studies. Given the low level of absorption, the reviewer has no concerns about reproductive toxicity.

7.1.15 Assessment of Effect on Growth

This product is not expected to have any effect on growth in pediatric subjects.

7.1.16 Overdose Experience

None. Overdosage is very unlikely given the small treatment area recommended and the low absorption of the drug.

7.1.17 Postmarketing Experience

None.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

There were a total of 484 Altabax patients in the safety database. Please see section 4.2 for a complete listing of all patients in all studies. This is the database used to evaluate safety. The safety data for the 2 clinical studies was combined.

In summary, there is adequate experience with the drug in impetigo in terms of overall numbers of patients and demographic subjects to provide a comprehensive picture of drug safety. [redacted]. The drug

exposure was sufficient to permit evaluation of possible toxicities which might be expected in normal use.

7.1.2.2 Demographics

Please see tables 7 and 22 above for a complete description of the demographics of the patients in the clinical studies.

7.1.2.3 Extent of exposure (dose/duration)

In the clinical studies, 484 patients were exposed to at least one dose of Altabax. The mean exposure for both studies was 10 applications for 5 days.

7.2.2 Description of secondary clinical data sources used to evaluate safety

7.2.2.1 Other studies

Not applicable.

7.2.2.2 .Postmarketing experience

Not applicable.

7.2.2.3 Literature

Not applicable.

7.2.3 Adequacy of overall clinical experience

The experience in testing of Altabax in impetigo is adequate given its short-term (5 day) use on restricted skin areas. [redacted] The possible adverse event profile has been well defined by the impetigo testing program. [redacted] The safety data [redacted] support for the safety of Altabax in impetigo.

7.2.4 Adequacy of special animal and/or in vitro testing

Please refer to [redacted] for information on animal and in vitro testing.

7.2.5 Adequacy of Routine Clinical Testing

Clinical test procedures, including adverse event reports and lab values were sufficient to adequately monitor potential adverse effects.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The metabolic and clearance pathways for this poorly absorbed topical drug have not been delineated.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The applicant has made adequate efforts to identify potential adverse effects, and no further studies are needed.

7.2.8 Assessment of Quality and Completeness of Data

The available data is adequate.

7.2.9 Additional Submissions, Including Safety Update

The 120 day safety update has been submitted. No new information on the safety of this drug has been generated.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

There are no specific safety concerns about the use of Altabax in impetigo. There are infrequent skin reactions which are associated with the use of any topical product. The only data limitation which should be mentioned is the generally recognized tendency of studies based in foreign countries to have lower rates of adverse event reporting than studies based in the U.S. [redacted] the adverse event reporting rate was about two times higher for U.S. based patients than foreign-based patients. Nonetheless, it has been established that Altabax is relatively safe for use when applied as directed.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.3.1 Pooled data vs. individual study data

Pooling data for Altabax across the placebo-controlled and sodium fusidate studies is justified by the similarity of use of Altabax in impetigo in both studies.

7.3.1.2 Combining data

Not applicable.

7.4.2 Explorations for Predictive Factors

7.4.3.2 Explorations for dose dependency for adverse findings

The adverse event rates seen in the impetigo studies vs. those seen in the [redacted] studies do not suggest any undetected toxicities which might reveal themselves during the marketing of the drug for impetigo. The adverse event reporting rate (all events = 19%) is similar to the 16-18% rate seen in non-U.S. based patients in [redacted].

7.4.2.2 Explorations for time dependency for adverse findings

This analysis was not performed, nor is is considered necessary since the drug is to be used for 5 days only.

7.4.2.3 Explorations for drug-demographic interactions

The analysis for success by demographic groups does not reveal any unusual results for varying demographic groups.

7.4.2.4 Explorations for drug-disease interactions

Given the low systemic absorption of Altabax, it is unlikely that drug-disease interaction will occur.

7.4.2.5 Explorations for drug-drug interactions

No studies of this type were performed in support of this NDA. [redacted]

7.4.3 Causality Determination

The only adverse events which can be evaluated as association with Altabax with any certainty are topical (irritation, etc.).

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The clinical studies establish that the dosage chosen by the sponsor is effective and does not cause undue toxicity. There are no unresolved dosing issues.

8.2 Drug-Drug Interactions

[redacted] discussion of possible drug-drug interactions.

8.3 Special Populations

No dosing considerations for special populations have been shown to be necessary.

8.4 Pediatrics

[redacted] A study in pediatric patients aged 2 to 9 months is needed to achieve compliance with the Pediatric Research Equity Act. The protocol for this study has been submitted for review and comments on the study design have been provided to the Applicant. The Applicant should be granted a deferral for submission of this data to December 31, 2008.

8.5 Advisory Committee Meeting

Not applicable.

8.6 Literature Review

Not applicable.

8.7 Postmarketing Risk Management Plan

Not applicable.

8.8 Other Relevant Materials

None.

9 OVERALL ASSESSMENT

9.1 Conclusions

The medical reviewer concludes that Altabax has been established as effective for the indication of impetigo up to 100 cm^2 in total area (up to 10 lesions) caused by *Staphylococcus aureus* and /or *Streptococcus pyogenes*. This conclusion is supported by a well controlled pivotal study comparing Altabax to placebo, both used BID for 5 days. Using the reviewer's preferred primary efficacy criterion of clinical success at the follow-up visit, Altabax had clinical success rates which were 35-45% higher than placebo in all analysis populations. Altabax was also superior to placebo in such secondary efficacy parameters as wound size, clinical success rate in microbiologically evaluable patients, and clinical response by various demographic variables.

The second pivotal study submitted in support of the impetigo indication was a comparison of Altabax and sodium fusidate ointment. This study is not acceptable as a pivotal efficacy study as follows:

A. Since sodium fusidate ointment is not approved in the U.S., the reviewer must regard it as a placebo and Altabax would have to be proven superior to it in order for the study to be successful. By the Applicant's analysis, the two products are not statistically dissimilar at follow-up, which is the reviewer's chosen primary efficacy parameter. Therefore, the study is not acceptable as a pivotal clinical study. It is acceptable as a well-performed supportive study.

B. Because the two test products were dissimilar in appearance and had different dosing regimens, the study is single-blind by design. The possibility of the evaluator being aware of which test product the patient received is much higher under these circumstances.

Based on the available information in this NDA and [redacted] Altabax is safe for use in impetigo. The active ingredient is poorly absorbed. Standard human skin testing does not suggest that Altabax has the potential for unusual skin irritation or sensitization. The adverse events reported in the clinical studies were infrequent. About 5% of the Altabax patients in the combined safety database for the impetigo studies had a drug related adverse event, which is similar to the rate seen in [redacted]

The adverse events seen were usually mild skin reactions which were reversible upon cessation of drug therapy. The safe use of Altabax will be facilitated by the relatively small skin area to be treated and by the limited (5 day) course of therapy.

9.2 Recommendation on Regulatory Action

Please see section 9.1 above. This NDA may be approved for the treatment of impetigo.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Not necessary or recommended, except for routine surveillance.

9.3.2 Required Phase 4 Commitments

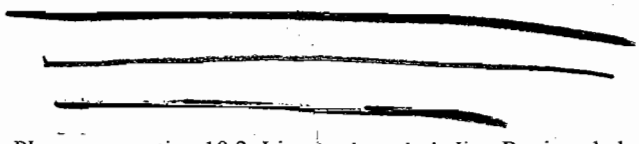
Not necessary or recommended.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

DMETS has approved use of the trade name Altabax. No Medication Guide or Patient Package Insert is necessary for the safe use of this product. The recommended labeling revisions concern the labeling submitted by the Applicant on February 13, 2007. This labeling provides for the impetigo indications.



Please see section 10.2, Line-by-Line Labeling Review, below for the complete recommended label for this product.

9.5 Comments to Applicant

The labeling comments found under section 10.2 should be transmitted to the sponsor.

16 Page(s) Withheld

_____ Trade Secret / Confidential

8 Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical- 4

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Bostwick
3/19/2007 11:35:56 AM
MEDICAL OFFICER

Jean Mulinde
3/19/2007 11:51:19 AM
MEDICAL OFFICER